End Stage Renal Disease: The Oral Component

Bots, C.P.

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Saliva, thirst and oral health in patients

on renal replacement therapy

Casper P. Bots

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End Stage Renal Disease: The Oral Component

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ter verkrijging van de graad Doctor aan
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door

Casper Peter Bots
geboren te Idaarderadeel

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Geprezen zij de Here.
Dag aan dag draagt Hij ons; die God is ons heil.

Psalm 68 : 10

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- the Department of Dental Basic Sciences, section Oral Biochemistry, Academic Center for Dentistry Amsterdam (ACTA), Vrije Universiteit and Universiteit van Amsterdam, Amsterdam, The Netherlands
- the Department of Nephrology, Institute for Cardiovascular Research, Vrije Universiteit Medical Center (VUMC), Amsterdam, The Netherlands
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- the Department of Clinical Epidemiology and Biostatistics, Vrije Universiteit University Medical Center (VUMC), Amsterdam, The Netherlands
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CONTENTS

1

GENERAL INTRODUCTION

BACKGROUND

The kidneys play an essential role in the maintenance of hemostasis by their capacity to remove metabolic waste products, electrolytes and water from the body. End stage renal disease (ESRD) occurs when the function of the kidneys is impaired towards 5-10% of the original capacity, defined by a reduction in glomerular filtration rate (GFR), and decreased creatinin clearance rate.

Over the last decades, the prevalence and incidence of ESRD has increased.[1] In 2001, a total of 9830 patients on kidney replacement therapy (dialysis and renal transplantation) were registered in the Netherlands. The incidence of patients with ESRD in 2001 was 100 *per million,* increases with age and male individuals are more commonly affected than females (www.renine.nl). The average survival of 2-, 5- and 10-years in Europe between 1980 and 1999 was 67, 35 and 11% in dialysis patients.[2] The most common causes of ESRD are chronic hypertension, glomerulonephritis, polycystic kidney disease, renovascular disease and diabetes mellitus.[1] The pivotal role of the kidneys in human metabolic homeostasis is exemplified by the fact that renal failure has been shown to result in anemia, hypertension, neuropathy, thyroid dysfunction and reduced libido.[3,4]

Patients with ESRD can rely on kidney replacement therapeutic modalities such as hemodialysis (HD), peritoneal dialysis (PD) or renal transplantation (NTx). During HD treatment (in 2001 one third of the ESRD patients), the blood is filtered by an artificial kidney. Access to the circulatory system is obtained through a surgically created arteriovenous shunt. In addition, erythropoietin is given regularly during the dialysis session and anticoagulants are administered. In general, HD treatment is done on a regular basis (performed every two till three days for four till five hours). In PD treatment (13% of the ESRD patients), the peritoneal membrane of the patients is used as an artificial kidney. Sterile dialysis fluid is introduced into the abdominal cavity for several hours, drained and refreshed several times a day (Continuous Ambulatory Peritoneal Dialysis = CAPD) or continuously at night (Continuous Cycler-Assisted Peritoneal Dialysis = CCPD). Kidney transplantation is, in general, a more patient friendly form of therapy, since the aim is to restore normal function and homeostasis. In the Netherlands, the average time for a ESRD patient to undergo renal transplantation is 4.5 year. Renal transplant patients (about half of the ESRD patients) receive their allografts from living or cadaveric donors. In 2001, 525 kidney transplantations were carried out in the Netherlands (364 cadaveric: 161 living donors). Acute and chronic rejection remains a major clinical hurdle despite recent advances in immunosuppressive strategies.[5]

Although kidney replacement therapies have proven to be successful in prolonging the life expectancy of ESRD patients, several limitations and long-term complications exist.[6] Since the majority of HD patients has no residual urine output, they have to maintain a fluid restricted diet to prevent fluid overload and are thus allowed to consume only approximately 500 mL per day. If patients do not adhere to the restriction in fluid intake, (chronic) fluid overload may

occur, which can result in hypertension, acute pulmonary edema, congestive heart failure and consequently death.[3,7-10] The interdialytic weight gain (IWG) can be used as an indicator of compliance to this fluid restricted diet.[11,12] IWG is expressed as the excess amount of fluid (in kg) removed during the dialysis.

Apart from the complications described above, PD is potentially complicated by peritonitis, which is a serious and sometimes lethal side effect.[13] Although transplantation is a permanent solution in 50% of ESRD patients, long term use of immunosuppressive medication can lead to side effects, e.g. gingival overgrowth, opportunistic infections and cancer.[14,15] In a retrospective analysis comprising 918 patients who had undergone a renal transplantation, 40% of the recipients had developed cancer after 20 years of immunosuppressive therapy.[16]

SALIVA, ORAL DRYNESS AND THIRST

Human saliva is a unique fluid, secreted by the major salivary glands (parotid, submandibular and sublingual glands) and by hundreds of minor salivary glands located in the palate, lip, cheek and tongue (Figure 1). Saliva is predominantly produced in the acinar cells of these glands divided into serous and mucous cells.[17] Saliva from the sublingual, labial and palatal glands are rich in high molecular weight mucins, in contrast to the parotid glands, which secrete a more watery or serous type of saliva. The submandibular saliva has a more seromucous character.

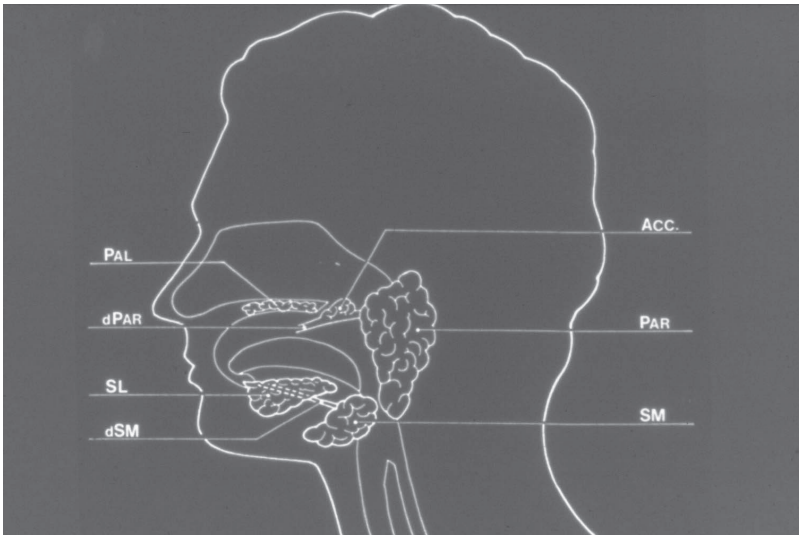

Figure 1. Anatomic location of the major human salivary glands. Pal, palatal glands; dPar, ductus parotidea; SL, sublingual gland; dSM, ductus submandibularis; Acc, accessory glands; PAR, parotid gland; SM, submandibular gland (Source: *collection Oral Biochemistry, ACTA*)

Unstimulated whole saliva (UWS) mostly consists of a mixture of saliva largely derived from the sublingual, submandibular and minor salivary glands.[18] The salivary flow rate of the parotid glands can be stimulated both by chewing or the application of e.g. citric acid. Saliva formed by the various salivary glands differs in biochemical composition. The mean output of amylase, for example, is higher by parotid glands compared to that of submandibular glands. The composition of whole saliva is therefore influenced by the net flow rate from the different types of salivary glands and by the various types of stimulation. For example, during salivary stimulation of the parotid gland, less sodium and bicarbonate will be resorbed in the glandular ducts, resulting in a higher sodium concentration.[19]

Under physiological conditions, approximately 500-1000 mL of saliva is secreted every 24 hours, and its main effect is lubricating and protecting all oral tissues.[19] In addition, saliva has been shown to exert anti-viral, anti-fungal and anti-bacterial capacity.[20-24] Salivary proteins such as mucins, glycoproteins and the bicarbonate buffer system in saliva all have protective functions as depicted in Figure 2.[25]

Hyposalivation is the objectively determined reduction of the salivary flow rate (unstimulated salivary flow rate ≤ 0.15 mL/min)[26] and can occur due to several reasons. The main reasons are radiotherapy, the presence of an autoimmune disease or the use of multiple medication.[22,27-29] Signs and symptoms of hyposalivation are reduced lubrication, difficulties with speaking, swallowing and eating as well as an increased urge for water intake to moisture the oral cavity. Due to reduced protection, patients with oral dryness are prone to microbial

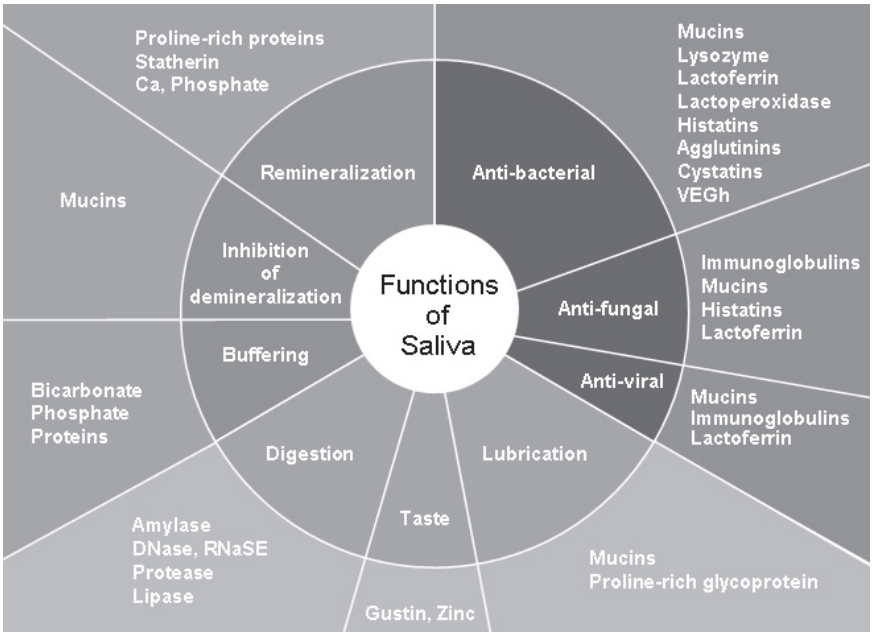

Figure 2. Functions of saliva. (Adapted from: Levine MJ, *Am NY Acad Sci* 1993; 694: 11-16)

colonization of the oral mucosa, which can result in an increased susceptibility for fungal infections and oral inflammations.[30,31]

Xerostomia has been defined as the subjective feelings of a dry mouth.[32] Reduced salivary flow rates and xerostomia are not exclusively linked to each other. In most subjects, xerostomia will occur when the salivary flow rate decreases to a level below 50% of the normal secretory capacity. [33] Xerostomia is known to negatively influence the patients' quality of life (QoL).[24,34] Patients with apparently normal salivary flow rates, however, may also suffer from xerostomia. This paradoxical finding is likely to be related with alterations of salivary composition.[35,36]

Thirst, the urge to drink, can occur as a consequence of both xerostomia and hyposalivation.[37,38] Besides a dry mouth, thirst is affected by many different factors including high concentration in plasma of sodium, potassium depletion, vasopressin, acute increases in plasma urea as well as psychological factors.[39-46]

SALIVA, ORAL DRYNESS AND THIRST IN ESRD

In HD patients, reduced salivary flow rate and thirst have been reported to be closely correlated.[47-53] In the study by Kho and co-workers, salivary flow rates in 22 HD patients and 22 controls were compared. The salivary flow rate measured on a non-dialysis day of the patients was statistically significantly lower than that of the controls (0.30 ± 0.18 versus 0.45 ± 0.25 mL/min respectively; $P < 0.05$).[49] In another study with 72 dialysis patients, stimulated whole saliva was collected before a HD session. The mechanically stimulated salivary flow rate was found to be significantly reduced in HD patients, compared with healthy controls (0.69 ± 0.31 versus 1.64 ± 0.44 mL/min, respectively $P < 0.001$).[54]

It should be noted that the circadian cycle has, under healthy conditions, also a large effect on salivary flow rate and dialysis treatment may influence this effect. Therefore, the above mentioned studies might be hampered by the moment of collection.[55,56]

Besides an effect on the salivary flow rate, it has been shown that renal replacement therapy such as HD could also affect the biochemical composition of saliva.[47,57,58] However, no large scale studies have been carried out to investigate the effect of NTx or PD on the salivary flow rates and composition. Patients with renal failure and consequently high urea concentrations in serum also display high urea levels in saliva, since urea is passively distributed from serum towards saliva.[58] Most studies on salivary flow rate and composition in dialysis patients have been carried out on a non-dialysis day. The salivary flow rate appeared to be reduced compared to controls.[49,50] In addition, a few studies have investigated the effect of dialysis on the composition of saliva and revealed a markedly decrease of urea and a small decrease of the anti-oxidant status in dialysis patients.[47,57]

In the literature, the prevalence of xerostomia in patients on hemodialysis ranges between 33 and 76%.[12,48,59] Besides xerostomia, thirst is one of the most frequently occurring symptoms in ESRD patients.[60,61] The combination of the fluid restricted diet, high plasma sodium concentration, psychological factors and acute increases in plasma urea may all contribute to perceived thirst.[39,62,63] No validated thirst assessment test was described in literature at the moment of beginning the studies presented in this thesis. We therefore developed a questionnaire for HD patients: the Dialysis Thirst Inventory (DTI).[12]

Since ESRD patients have to deal with oral dryness it is conceivable that xerostomia and thirst are factors that contribute to the intake of fluid in HD patients and – consequently – to the IWG. We hypothesize that oral dryness is associated with the urge to drink or to moisten the mouth and throat.[12]

ESRD AND ORAL HEALTH

In general, oral health is influenced by many factors. Diet, level of oral hygiene, use of fluoride, presence of commensally microorganisms, genetic factors, ageing, systemic diseases, medication and the amount and 'quality' of saliva all have been described to play a pivotal role in the net state of oral health.[21,27,64] In ESRD patients, the oral health could also negatively be affected by the underlying pathology, the dialysis treatment, oral dryness or an altered salivary composition.[47,49,54,65,66] Renal failure is associated with vomiting, oral malodor and xerostomia which could all affect the oral health of these patients.[60,67] Oral manifestations that have been reported include mucosal lesions, oral infections, dental anomalies and bone lesions due to secondary hyperparathyroidism, gingivitis, mucosal pallor and lesions, an altered microbiological environment, tooth mobility, malocclusion and an increased risk for dental erosion.[65-72]

Chronic dialysis could retract the attention from oral health towards more important matters, regarding life and death. Several studies have reported that the oral self care of ESRD patients is reduced compared to controls.[66,73] On the other hand, maintaining oral health at a high level is in any case very important for those HD patients waiting for a renal transplant since oral pathologies or infections could jeopardize the success of the transplantation.[74-76] Conflicting data have been reported in literature on the effect of chronic dialysis therapy on oral health status.[48,66,77,78] In a study, comprising a cohort of 53 hemodialysis patients, the number of decayed missing and filled teeth (DMFT) and the Loss of Periodontal Attachment (LPA) did not differ from an age- and gender-matched controlgroup.[48] In ESRD patients, both increased and decreased rates of dental caries have been reported.[66,68,79] A study of Bayraktar and colleagues showed no difference for the number of decayed, missing or filled teeth between adult HD patients and controls.[54] Increased salivary urea levels could enhance calculus formation, but on the other hand also contribute to the remineralization of dental enamel

leading to lower caries incidence, which has been shown for example in children with chronic renal failure (CRF).[80]

AIMS AND OUTLINE OF THE THESIS

This thesis comprises a number of studies aiming to provide insight in the acute and long term effects of dialysis on oral dryness (salivary flow rate and xerostomia), thirst and oral health in ESRD patients. Furthermore, the aim was to assess the relationship between oral dryness (defined as reduced salivary flow rates and xerostomia), thirst and IWG in patients on hemodialysis, and to investigate potential therapies to reduce oral dryness and consequently IWG.

First, the acute effects of HD on the salivary flow rate and composition were studied before, during and after a dialysis session (Chapter 2). To unravel the association between oral dryness and fluid-intake in HD patients, we investigated in HD patients the relation between IWG, thirst and oral dryness (Chapter 3).

The oral health of dentate ESRD patients on dialysis treatment was assessed and compared to a healthy reference group (Chapter 4). In a two-year follow up study, the oral health, salivary flow rates, thirst and xerostomia were compared of those patients that received a renal transplant with those remaining on dialysis (Chapter 5).

Since it appeared that chewing could stimulate the salivary flow rate in healthy subjects (Appendix) and HD patients, we investigated the effect of chewing gum and artificial saliva on IWG, salivary flow rate, xerostomia and thirst in a crossover study (Chapter 6). The more subjective reports and preferences of the HD patients between chewing gum and artificial saliva were explored in Chapter 7. Finally, in Chapter 8, we discuss the results of our studies.

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2

ACUTE EFFECTS OF HEMODIALYSIS ON SALIVARY FLOW RATE AND COMPOSITION

Casper P. Bots, Henk S. Brand, Enno C.I. Veerman, Marianne Valentijn-Benz, Yvonne M.C. Henskens, Robert M. Valentijn, Pieter F. Vos, Joost A. Bijlsma, Piet M. ter Wee, Barbara M. Van Amerongen, Arie V. Nieuw Amerongen

Submitted

ABSTRACT

Background

Major systemic changes occur during hemodialysis (HD), which could affect the flow rate and biochemical composition of saliva. Therefore, the aim of this study was to evaluate acute effects of HD on the salivary flow rate, pH and biochemical composition before, during and after completion of a dialysis session.

Methods

In 94 HD patients, unstimulated whole saliva (UWS) and chewing-stimulated whole saliva (CH-SWS) were collected immediately before, during and after a dialysis session. Salivary flow rate, pH, concentration of total protein, albumin, cystatin C and of sodium, potassium and urea were measured.

Results

Hemodialysis had an acute stimulating effect on the salivary flow rate (UWS *before* = 0.30 ± 0.22 mL/min; UWS *during* = 0.39 ± 0.25 mL/min; $P < 0.005$). The mean pH of UWS showed a small but significant increase during dialysis (pH *before* = 7.16 ± 0.58 to pH *during* = 7.31 ± 0.49; $P < 0.005$). The concentrations of the biochemical constituents (total protein, albumin, cystatin C and S-IgA) in whole saliva changed markedly, but no significant difference in output was found. Also the electrolyte concentration did not change during dialysis. The level of urea in CH-SWS declined with 40% (urea *before* = 25.6 ± 6.4 mmol/L, urea *during* = 15.3 ± 4.5 mmol/L).

Conclusions

This study shows that HD has significant acute effects on both salivary secretion rate and protein concentrations in saliva. We conclude that the observed changes in salivary concentrations and proteins are mainly due to an increased watery secretion from the salivary glands.

INTRODUCTION

Patients with end stage renal disease (ESRD) have to undergo kidney replacement therapy such as hemodialysis (HD), peritoneal dialysis or renal transplantation. The aim of HD treatment is to remove metabolic waste products such as urea, and to remove excess fluid from the body of the patients to restore circulatory volume. HD treatment, which is carried out on average three times a week during a three till four hours session, has major effects on the serum composition and fluid-balance. Furthermore, it had been shown to affect the flow rate and biochemical composition of saliva.[1-3]

HD patients show reduced unstimulated and mechanically stimulated salivary flow rates compared to controls, both before dialysis sessions and on interdialytic days.[4-8] In chapter 3, we will demonstrate that hyposalivation and xerostomia are correlated with thirst in HD patients.[9] Therefore, it seems feasible to presume that reduced thirst feelings during and after HD treatment could potentially be caused by a concomitantly increase of salivary flow rate. In addition, several serum components such as albumin or urea are in equilibrium with the concentration in saliva. Therefore, saliva can potentially be used to monitor changes in concentration of serum proteins and electrolytes.[10]

However, until now it is still unclear whether a HD session has acute effects on the salivary flow rate and composition. Therefore, the aim of this study was to evaluate several salivary parameters including flow rate, pH and biochemical composition before, during and after completion of a HD session.

MATERIALS AND METHODS

Participants

Ninety-four patients with ESRD undergoing HD treatment were recruited from four different dialysis centers. Inclusion criteria were ≥ 18 years old and ≥ three months on HD. The subjects were dialyzed three to four times a week for approximately three hours. Each subject signed an informed consent and agreed to participate in a follow-up study to investigate the effect of HD treatment on saliva and oral health.[9] This study was approved by the Medical Ethical Committee of the Vrije Universiteit Medical Center, Amsterdam, The Netherlands.

Data collection

Demographic variables were assessed with a questionnaire, as described in Chapter 3.[9] Clinical data with regard to hemodialysis were retrieved from a database (Diamant®, Diasoft, Leusden, the Netherlands) and included the primary renal disease (according to the classification of the European Dialysis and Transplantation Association-European Renal Association (EDTA-ERA)) and time of treatment on HD[11]. The efficiency of dialysis was expressed as the

Kt/V_{urea} (removal of urea by dialysis a week). Systolic (SBP) and diastolic blood pressure (DBP) was measured before and after the hemodialysis session.

Collection of saliva

Unstimulated whole saliva (UWS) and chewing-stimulated whole saliva (CH-SWS) were collected immediately before a dialysis session (*before = baseline)*, one hour after the start of the dialysis (*during)* and directly after completion of the dialysis session *(after).* All subjects were instructed to refrain from smoking, eating, drinking and tooth brushing for one hour prior to the three saliva collection periods. In each patient, the samples were collected during one dialysis session.

UWS was collected according to the spitting method[12] with small modifications.[9,13] Before collection, the mouth was rinsed with tap water. The collection started with the instruction to void the mouth of saliva by swallowing. Subsequently, saliva was allowed to accumulate on the floor of the mouth and the subjects were instructed to spit out into the pre-weighed test tubes every 30 seconds. Each saliva collection period was five minutes.

CH-SWS was collected for five minutes using a piece of parafilm (5 x 5 cm; 0.30 g; Parafilm "M", American National CAL, Chicago, USA). During the saliva collection period, the subjects chewed at their own natural pace and stimulated saliva was collected in the same way as the unstimulated samples.

The volume of saliva was determined gravimetrically (assuming 1 g = 1 mL) and the pH was determined within five minutes after saliva collection (Sentron pH-system 1001, Roden, The Netherlands). Hereafter, saliva was homogenized by vigorous shaking for one minute using a vortex mixer and centrifuged (10 minutes at 10 000 g, room temperature), to eliminate cellular debris. The supernatant was divided into 500 µL aliquots, frozen at -70 °C and stored at -20 °C until further analysis. The total time for collection and preparation of the saliva samples took approximately 30 minutes, during which the test tubes were kept on ice.

Biochemical analysis of saliva

The total protein concentration in saliva was determined by the bicinchoninic acid method and expressed as mg/L. Bovine serum albumin was used as a standard.[14]

Albumin, a serum protein present in saliva, was quantified with a sandwich enzyme-linked immunosorbent assay (ELISA), as previously described.[15] Briefly, high-affinity microtiter plates (Greiner, Hannover, Germany) were coated with 1.7 µg/mL of purified immunoglobulins against human albumin (Dakopatts, Glostrup, Denmark). Bound albumin was detected using peroxidase-conjugated rabbit antihuman albumin (Dakopatts). The optical density at 490 nm was measured with an MR 7000 microtiter plate reader (Dynatech, Billinghurst, UK).

The protein cystatin C, present in serum and saliva, was determined in saliva using a sandwich ELISA.[16] Secretory immunoglobulin A (S-IgA), a protein secreted by the parotid and

submandibular salivary glands, was quantified using the method described by Bosch and co-workers.[13]

Sodium, potassium and urea (urea nitrogen) were determined in saliva using an automated clinical chemistry analyzer (Roche/Hitachi Modular P800, Roche Diagnostics, Mannheim, Germany). Sodium and potassium were determined using ion-selective electrodes.[17] The test principle for the urea determination was an enzymatic procedure using the coupled urease/glutamate dehydrogenase enzyme system optimized to permit kinetic (fixed time) measurements.[18] The electrolyte concentrations were expressed as mmol/L.

All saliva samples were assayed in duplicate. Output of saliva components was calculated by multiplying the salivary flow rate (mL/min) with the concentration (mg/mL), resulting in mg/min or mmol/min.

Statistical methods

Data are presented as mean ± SD. Since the salivary flow rate and the biochemical constituents showed a skewed distribution, these data were logarithmically transformed ($\log^{10}$) before statistical analysis. For readability, the original (untransformed) data are presented. Overall differences of the measured variables between the three measurements were analyzed applying repeated-measures multivariate analysis of variance (MANOVA). We applied MANOVA three times; once for the differences between first and second measurement, once for the differences between second and third measurement and finally for the difference between the first and last measurement. When the multivariate difference showed statistical significance, differences between the individual variables were further explored by paired *t*-tests as post-hoc procedures. Data at baseline (*before* dialysis) were stratified with regard to time on dialysis (≤ 24 and > 24 months) and analyzed using analysis of variance (ANOVA). Statistical analysis was performed using the statistical software package SPSS (version 10.0, SPSS Inc., Chicago, IL, USA). Levels of significance were set at $P < 0.05$.

RESULTS

Patients demographics

Ninety-four patients with end-stage renal disease (ESRD) undergoing hemodialysis, 64 men (mean age 54.8 ± 15.5 years) and 30 women (mean age 59.5 ± 18.7 years) participated in this study. The clinical data are presented in Table 1. The mean time of treatment on hemodialysis was 35.8 ± 31.0 months, (range 3–188 months) and the Kt/V_{week} was 3.6 ± 1.1. The causes of chronic renal failure in the study population were renal vascular disease due to hypertension (16.0%), polycystic kidneys adult type (11.7%), glomerulonephritis (10.6%), miscellaneous (22.3%), and unknown (39.4%).

Table 1. Clinical data of HD patients (n = 94)

	Mean (SD)	Range
Mean age (year)	56.4 (16.7)	20 – 85
Mean time since first dialysis (months)	35.8 (31.0)	3 – 188
Mean IWG (kg)	2.2 (1.3)	0.0 – 5.6
Mean Kt/V_{week}	3.6 (1.1)	0.9 – 6.0
Mean SBP_{before} (mm Hg)	146 (22)	90 – 195
Mean DBP_{before} (mm Hg)	81 (13)	50 – 113

Abbreviations are: IWG, interdialytic weight gain; Kt/V, removal of urea by dialysis a week, V, volume of distribution of urea estimated as 55% of body weight; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Flow rate and composition of unstimulated (UWS) and chewing stimulated (CH-SWS) saliva *before*, *during* and *after* dialysis (n = 94)

	UWS			CH-SWS		
	Before	*During*	*After*	*Before*	*During*	*After*
Flow rate (mL/min)	0.30 (0.23)	0.39 (0.25)[a]	0.41 (0.25)[a]	1.05 (0.71)	1.27 (0.83)[a]	1.23 (0.74)[a]
pH	7.2 (0.6)	7.3 (0.5)[a]	6.7 (0.5)[a,b]	7.3 (0.5)	7.4 (0.9)	6.9 (0.9)[a]
Total protein (mg/L)	2413 (1080)	1968 (1185)[a]	1624 (1127)[a,b]	2215 (1171)	1502 (1108)[a]	1354 (816)[a,b]
Albumin (mg/L)	68.1 (60.5)	60.8 (58.5)[a]	42.9 (45.3)[a,b]	55.2 (62.0)	37.3 (47.9)	30.9 (30.2)[a,b]
Cystatin C (units)	1.6 (1.7)	1.3 (1.5)[a]	1.3. (1.1)[a]	1.1 (1.0)	0.8 (0.6)[a]	1.0 (0.6)
S-IgA (mg/L)	385 (293)	320 (266)	216 (168)[a]	301 (380)	259 (432)[a]	182 (179)[a]
Sodium (mmol/L)	14.0 (9.6)	12.6 (8.0)	11.3 (7.5)[a]	15.8 (11.8)	15.8 (12.5)	13.3 (11.3)[a,b]
Potassium (mmol/L)	32.2 (11.1)	29.6 (10.7)	26.8 (7.9)	35.0 (11.5)	30.6 (8.5)	29.4 (7.8)
Urea (mmol/L)	24.7 (7.0)	17.4 (5.1)[a]	10.5 (3.4)[a,b]	25.6 (6.4)	15.3 (4.5)[a]	9.6 (3.2)[a,b]

Data are expressed as mean (SD) *before*, *during* and *after* dialysis (n = 94).

[a] = significant difference with measurement *before* dialysis ($P < 0.05$)

[b] = significant difference with measurement *during* dialysis ($P < 0.05$)

Salivary flow rate and pH

The mean unstimulated salivary flow rate increased significantly with 30% within the first hour of dialysis and remained increased after the dialysis session (UWS *before* = 0.30 ± 0.22 mL/min; UWS *during* = 0.39 ± 0.25 mL/min; UWS *after* = 0.41 ± 0.25 mL/min, $P < 0.001$), see Table 2. The stimulated salivary flow rate (CH-SWS) showed a 17% increase during the first hour of dialysis and remained constant thereafter. Salivary flow rates of UWS and CH-SWS were well within the range of the normal salivary flow rate values for healthy subjects (reference value UWS = 0.30 ± 0.20 mL/min; pH = 6.7 ± 0.7).[19]

At baseline (*before*), male subjects had significantly higher flow rates of both UWS *before* (0.34 ± 0.22 mL/min) and CH-SWS *before* (1.21 ± 0.69 mL/min) compared to female subjects (UWS *before* = 0.21 ± 0.21 mL/min; CH-SWS *before* = 0.74 ± 0.6 mL/min, $P < 0.01$).

The mean pH of UWS showed a small but significant increase during dialysis, pH *before* = 7.16 ± 0.58 to pH *during* = 7.31 ± 0.49 ($P < 0.005$), but dropped to pH *after* = 6.68 ± 0.54 (see Table 2). The mean salivary pH of CH-SWS showed a similar small initial increase (pH = 7.34 ±

Table 3. Output of biochemical components of unstimulated (UWS) and chewing stimulated saliva (CH-SWS) *before*, *during* and *after* dialysis (n = 94)

	UWS			**CH-SWS**		
	Before	*During*	*After*	*Before*	*During*	*After*
Total protein (mg/min)	657 (464)	663 (472)	575 (403)	1970 (1153)	1537 (991)[a]	1393 (834)[a]
Albumin (mg/min)	15.6 (14.5)	17.5 (15.1)	13.8 (14.2)[b]	39.8 (31.9)	31.9 (26.3)[a]	29.4 (25.3)[a]
Cystatin C (units/min)	0.5 (0.7)	0.4 (04)	0.6 (0.6)	1.1 (1.2)	1.1 (1.2)	1.3 (1.3)[a,b]
S-IgA (mg/min)	90.2 (76.2)	103.6 (93.0)	79.0 (63.5)	220.9 (3.7)	201.5 (172.0)	171.4 (136.7)[a,b]
Sodium (mmol/min)	4.4 (4.6)	4.1 (4.3)	3.7 (4.2)[a]	4.4 (4.4)	4.5 (4.5)	3.7 (4.1)[a,b]
Potassium (mmol/min)	10.7 (7.8)	9.7 (6.9)	8.9 (6.4)[a]	9.9 (7.2)	8.9 (6.7)	8.7 (6.7)
Urea (mmol/min)	8.5 (6.5)	5.8 (4.2)[a]	3.5 (2.7)[a,b]	7.5 (5.2)	4.5 (3.4)	2.9 (2.3)[a,b]

Output (mg/min; mmol/min) is expressed as mean (SD).

[a] = significant difference with measurement before dialysis ($P < 0.05$)

[b] = significant difference with measurement during dialysis ($P < 0.05$)

0.48 *before* to pH = 7.39 ± 0.90 *during* dialysis), although no statistical differences were found. After dialysis, the salivary pH of CH-SWS was decreased till pH = 6.87 ± 0.86 ($P < 0.001$).

The total period on dialysis (≤ 24 months; > 24 months) had no effect on either the salivary flow rate or pH of both UWS and CH-SWS (data not shown).

Concentration and output of biochemical constituents

One hour after the start of the dialysis session (*during*), the concentration of total protein, albumin, cystatin C and S-IgA was declined in UWS and remained reduced throughout the dialysis session, see Table 2. In CH-SWS, the concentration of total protein, albumin, cystatin C and S-IgA declined in the first hour of dialysis and remained declined *after* dialysis.

However, the output of protein constituents in UWS (total protein, albumin, cystatin C and S-IgA) did not differ after one hour from the start of the dialysis treatment. Also no differences were observed comparing the protein output *before* and *after* dialysis, see Table 3.

The concentration of sodium and potassium in UWS and CH-SWS during HD did not change compared to the levels before dialysis. However, *after* dialysis the sodium concentration in both UWS and CH-SWS decreased significantly, see Table 2. On the other hand, the output of sodium and potassium did not change in the first hour of dialysis. After dialysis, the output was significantly decreased, compared to the levels *before* dialysis

The average concentration in UWS of urea, a salivary constituent distributed by passive diffusion, decreased significantly by 30%, *during* dialysis. In CH-SWS the average decline *during* dialysis was even by 40% (urea *before* = 25.6 ± 6.4 mmol/L, urea *during* = 15.3 ± 4.5 mmol/L), see Table 2. The output of urea in UWS and CH-SWS *after* dialysis decreased on average with 60%, compared to the output *before*.

DISCUSSION

To our knowledge, this is the first large-scale study to investigate acute effects of hemodialysis on the salivary flow rate and composition of saliva. It was found that HD treatment had an acute stimulating effect on the salivary flow rate. The concentrations of the biochemical constituents in whole saliva changed markedly, although the average output in absolute terms remained relatively stable.

Only a few studies exist in which saliva of HD patients had been investigated. Unfortunately, two studies which investigated salivary variables before and after HD, did not provide salivary flow rate values, so that only concentrations could be compared.[10,20] Other studies in which saliva was collected *before* dialysis showed reduced flow rates of CH-SWS in HD patients (0.69 ± 0.31 mL/min) compared to healthy controls (1.64 ± 0.44 mL/min).[4,5] Citric acid (2%) stimulated salivary flow rates in HD patients on interdialytic days also tended to be decreased in HD patients compared to controls.[8] The findings of Kho and colleagues, who investigated the flow rate of UWS on a interdialytic day (0.30 ± 0.18 mL/min), are comparable to our findings of UWS *before* HD treatment (UWS *before* = 0.30 ± 0.23 mL/min).[7] In our study, both the unstimulated and chewing stimulated salivary flow rates *before* dialysis were well within the range of normal salivary flow rates of healthy subjects.[19]

The total protein concentration decreased significantly comparing *before* and *after* dialysis. This observation is in accordance with the study of Meucci and co-workers in which a trend was observed for reduced protein levels after dialysis (3.3 ± 3.9 mg/L) compared to before (5.5 ± 6.2 mg/L).[20] Although the salivary proteins measured in our study may differ in origin (serum, serum/saliva and saliva), the protein concentrations in saliva decreased during and after HD treatment. The relative contribution of albumin and S-IgA to the total protein concentration did not differ before and after dialysis in UWS and CH-SWS (data not shown). This illustrates that the level of albumin or S-IgA does not influence the total protein concentration in saliva, suggesting that the salivary glands maintain a normal function and no basement membrane defect seems to be present in HD patients.[2]

Under normal physiological circumstances, the composition of saliva differs from that in serum with respect to several constituents. Saliva secretion is primarily controlled by the mechanisms for sodium and chloride secretion, since fluid transport follows electrolyte transport. As the salivary flow rate increases, saliva passes through the striated ducts before re absorption of NaCl is complete. Therefore, the sodium and bicarbonate concentrations increase with increased flow rates, resulting in a higher salivary pH.[19]

Table 4 provides reference values for both whole human saliva and serum in healthy individuals. At all the time points in our study, the potassium concentration in UWS and CH-SWS maintained unchanged, which was expected and which is in agreement with an earlier study among children on hemodialysis.[10] In our study, the increased salivary flow rate did not correlate, however, with an increased salivary sodium concentration. This may be explained by

Table 4. Reference values of pooled unstimulated whole saliva (UWS ; n = 10) and plasma

	UWS	Plasma
Total protein (mg/L)	1057	60000-80000
Albumin (mg/L)	61	35000-55000
Cystatin C (mg/L)	1.1	1.1
S-IgA (mg/L)	138	-
IgA (mg/L)	194	800-3100
Sodium (mmol/L)	12.2	135-145
Potassium (mmol/L)	22.7	4.0
Urea (adults ; mmol/L)	5.7	5.0

the fact that HD patients are dialyzed against solutions containing sodium bicarbonate or acetate solutions, which could have influenced the electrolyte management in the salivary glands. Therefore, we conclude that the observed changes in salivary concentrations and proteins are mainly caused by the diluting effect of an increased fluid flow during dialysis instead of an altered protein secretion during dialysis.

In our study, the urea concentration of saliva was elevated *before* dialysis (24.7 ± 7.0 mmol/L), decreased significantly *during* the HD session and was the lowest *after* dialysis (10.5 ± 3.4 mmol/L). These changes are in accordance with other biochemical studies measuring the urea levels before and after HD treatment.[2,10] This illustrates that urea diffuses passively from the serum through the salivary glands, suggesting that the decrease in salivary urea concentration during HD treatment potentially could be used to monitor the efficacy of HD treatment.

Several other mechanisms and underlying factors potentially affecting the salivary flow rate could be explored. The salivary flow rate might be influenced by changes in blood pressure during dialysis. Due to an increased extra cellular fluid volume before HD, most patients have to deal with hypertension. In patients without chronic renal failure, hypertension *per se* is not related to the salivary flow rate.[21,22] During the HD sessions, on average 2.2 liter of excess fluid was removed. Under normal conditions, a reduction of plasma volume leads to a reduction in the secretion of saliva.[23,24] Our results show, however, that the opposite takes place during HD treatment.

An alternative hypothesis for the increased salivary flow rate might be an altered aquaporine expression in the salivary glands due to HD treatment. Aquaporines (AQP) are water-selective channels that are responsible for the transport of small uncharged molecules such as water through cell membranes. In patients with primary Sjögren's syndrome, the expression of AQP-1 in myoepithelial cells surrounding salivary acini is decreased by 38%, which might contribute to the reduced salivary flow rates of those patients.[25] The potential role of AQP is supported by the observation that changes in plasma osmolality during HD induces AQP-1 expression on the membrane of intact red blood cells.[26] However, an effect in the salivary glands was not studied.

We realize that our results may be biased by several factors. Since acute stress reduces the salivary flow rate, it might be possible that due to the relaxation during the hemodialysis session the salivary flow rate increased. Reduced flow rates could also be influenced by the time of measurement during the day.[27] As described in Chapter 3, no diurnal differences in saliva secretion rates were observed between HD patients treated in the morning versus those treated in the afternoon.[9]

CONCLUSION

This study shows that HD has significant acute effects on both salivary secretion rate and protein concentrations in saliva.

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3

INTERDIALYTIC WEIGHT GAIN IN PATIENTS ON HEMODIALYSIS IS ASSOCIATED WITH DRY MOUTH AND THIRST

Casper P. Bots, Henk S. Brand, Enno C.I. Veerman, Marianne Valentijn-Benz, Barbara M. Van Amerongen, Robert M. Valentijn, Pieter F. Vos, Joost A. Bijlsma, Pieter D. Bezemer, Piet M. ter Wee, Arie V. Nieuw Amerongen

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ABSTRACT

Background

Patients receiving hemodialysis (HD) have to maintain a fluid-restricted diet. Severe thirst can induce non-compliance to this diet, resulting in an increase of interdialytic weight gain (IWG = weight predialysis minus postdialysis) associated with poor patient outcomes. Since oral dryness may contribute to experienced thirst, we investigated the possible relation between thirst, salivary flow rate, xerostomia and IWG.

Methods

Unstimulated (UWS) and stimulated (CH-SWS) whole saliva were collected from 94 HD patients (64 men: 54.8 ± 15.5 years; 30 women: 59.5 ± 18.7 years). Secretion rates of saliva were determined gravimetrically. Xerostomia was assessed with a validated Xerostomia Inventory (XI) and thirst with a newly developed Dialysis Thirst Inventory (DTI).

Results

Before dialysis, 36.2% of the patients had hyposalivation (UWS ≤ 0.15 mL/min). The XI scores had a positive relation with IWG ($r = 0.250$, $P < 0.001$). Gender and age differences were observed for thirst, salivary flow rates and xerostomia. The prevalence and severity of thirst and xerostomia were greater in younger subjects. Patients with urine-output did not differ from those without urine-output with respect to thirst, xerostomia and IWG. Correlations were found between thirst (DTI) and both IWG and xerostomia (XI) ($r = 0.329$, $P < 0.001$, respectively; $r = 0.740$, $P < 0.001$). Other correlations were observed between xerostomia and both the salivary flow rate and total number of medications ($r = -0.252$, $P < 0.05$, respectively; $r = 0.235$, $P < 0.05$).

Conclusions

In HD patients, xerostomia (XI) and thirst (DTI) are associated with a higher IWG. Our data provide evidence that, in HD patients, xerostomia is related to both salivary flow rate and thirst (DTI).

INTRODUCTION

Patients with end stage renal disease (ESRD) on hemodialysis (HD) have to maintain a fluid restricted diet to prevent fluid overload.[1] During hemodialysis excess fluid is removed to normalize extracellular fluid volume and blood pressure. For many HD patients, however, it is difficult to adhere to this fluid restriction. Chronic fluid overload can result in hypertension, acute pulmonary edema, congestive heart failure and premature death.[2-6] The interdialytic weight gain (IWG) is an indicator of compliance to the fluid restricted diet, and is influenced by social and psychological factors, but foremost by physical factors like excessive thirst.[3,4,6-8]

Thirst or "the urge to drink" is affected by many different factors including sodium intake, high plasma sodium, potassium depletion, angiotensin II, acute increases in plasma urea, low dry weight (postdialysis hypovolemia) and psychological factors.[7-10] Besides thirst, a subjective feeling of a dry mouth (xerostomia) could also be a potential important stimulus for water intake.[11-13] Patients with xerostomia caused by radiation therapy, for example, report an increased water consumption in order to facilitate eating, articulation and speech.[14] Xerostomia has also been reported in patients on HD.[15] In addition, other studies showed impaired saliva secretion in HD patients compared to healthy controls.[16-21] Therefore, it is conceivable that xerostomia is one of the factors that contributes to the intake of fluid of HD patients and – consequently – to the IWG. The aim of the present study was to establish whether aspects of oral dryness, in particular salivary flow rate and xerostomia, are related to thirst and IWG in HD patients.

METHODS

Participants

ESRD patients, undergoing HD for at least three months, were recruited from four different dialysis centers. Ninety-four patients on HD gave informed consent for this study, which was approved by the Medical Ethical Committee of the Vrije Universtiteit Medical Center, Amsterdam, The Netherlands.

Age, gender, level of education, ethnic background, smoking habits, and use of alcohol were assessed with a questionnaire. Clinical data with regard to HD were retrieved from patient files in each participating center and are presented in Table 1. The pathology causing the chronic renal failure was classified according to the European Dialysis and Transplantation Association-European Renal Association.[22] The medication of the patients was categorized as potentially causing salivary hypofunction (putatively xerogenic) or not (nonxerogenic).[23,24] Patients were weighed before and after a dialysis session. IWG was defined as the amount of fluid (kg) removed during the session (weight predialysis minus weight postdialysis) with the

Table 1. Clinical data (n = 94)

	Mean (SD)	Range
Mean age (years)	56.4 (16.7)	20 – 85
Mean time since first dialysis (months)	35.8 (31.0)	3 – 188
Mean IWG (kg)	2.2 (1.3)	0.0 – 5.6
Mean Kt/V_{week}	3.6 (1.1)	0.9 – 6.0
Mean SBP (mm Hg)	146 (22)	90 – 195
Mean DBP (mm Hg)	81 (13)	50 – 113
Mean number of systemic medication (n)	9.8 (3.7)	3 – 18
Mean number of xerogenic medication (n)	1.0 (1.0)	0 – 4

Abbreviations are: IWG, interdialytic weight gain; Kt/V, removal of urea by dialysis a week, V, volume of distribution of urea estimated as 55% of body weight; SBP, systolic blood pressure; DBP, diastolic blood pressure.

assumption that all the weight gained in the previous interdialytic interval was lost during the dialysis session.[5,25]

Saliva collection

Unstimulated and chewing-stimulated saliva samples were collected before HD. All subjects were instructed to refrain from smoking, eating, drinking and tooth brushing for one hour prior to the saliva collection.

Unstimulated whole saliva (UWS) was collected according to the spitting method[26] with some small modifications.[27] Several minutes before collection, the participants rinsed their mouth with tap water. The collection started with the instruction to void the mouth of saliva by swallowing. Subsequently, saliva was allowed to accumulate in the floor of the mouth and the subjects were instructed to spit out into pre-weighed test tubes every 30 seconds. The saliva collection period was five minutes.

Chewing-stimulated whole saliva (CH-SWS) was collected for five minutes using a tasteless piece of parafilm (5 x 5 cm; 0.30 g; Parafilm "M", American National CAL, Chicago, USA). During the saliva collection period, the subjects chewed at their natural pace. The mechanically stimulated saliva was also spitted out into preweighed test tubes every 30 seconds for five minutes.

Saliva volumes were determined gravimetrically (assuming 1 g = 1 mL). Salivary hypofunction was defined as ≤ 0.15 mL/min UWS.[28]

Assessment of xerostomia and thirst

During the dialysis session, all participants completed the Dutch translation of the validated Xerostomia Inventory (XI), which consists of 11 items, each with a five-point Likert-scale (never = 1 to very often = 5), see Table 2.[29,30] Examples of items from the XI are "My mouth feels dry", "I have difficulty in eating dry foods" and "I sip liquids to aid in swallowing food". The responses to the 11 items were summed, which results in an individual XI score for each patient that ranges from 11 (no dry mouth) to 55 (extremely dry mouth).

Table 2. Items of the the Xerostomia Inventory (XI), the Dialysis Thirst Inventory (DTI) and the proportion of patients' answers (%) for each item divided in three categories

Xerostomia Inventory	**Never/ almost never**	**Occasionally**	**Fairly often/ very often**
I sip liquid to aid in swallowing food	38.7	29.0	32.3
My mouth feels dry when eating a meal	57.0	21.5	21.5
I get up at night to drink	53.8	24.7	21.6
My mouth feels dry	25.8	44.1	30.1
I have difficulty in eating dry foods	47.8	20.7	31.6
I suck sweets or cough lollies to relieve dry mouth	53.3	21.7	25.0
I have difficulties swallowing certain foods	67.0	22.0	10.0
The skin of my face feels dry	44.0	18.7	37.4
My eyes feel dry	65.6	19.4	15.0
My lips feel dry	30.1	34.4	35.5
The inside of my nose feels dry	62.6	20.9	16.5
Dialysis Thirst Inventory			
Thirst is a problem for me	30.4	30.4	39.1
I am thirsty during the day	14.1	38.0	47.8
I am thirsty during the night	43.5	27.2	29.3
My social life is influenced because of my thirst feelings	61.9	15.2	22.8
I am thirsty *before* dialysis	35.1	23.4	41.6
I am thirsty *during* dialysis	48.1	27.3	24.7
I am thirsty *after* dialysis	48.1	22.1	29.9

The Dialysis Thirst Inventory (DTI) was newly developed and used to quantify the perceived thirst. The DTI is a questionnaire with seven items (see Table 2). Each items has a five-point Likert type scale (never = 1 to very often = 5). The scores are summed, and provide a DTI score ranging from seven (no thirst) to 35 (very thirsty). In order to determine whether the items of the DTI represented one construct, a factorial analysis was carried out. This revealed one factor with an Eigen value of 3.98, which explained 56.9% of the variance of the items. The Chronbach's alpha for the DTI was 0.87.

When the subjects reported "occasionally" till "very often" on an item from either the XI or DTI, it was judged as 'present'. In all other cases, "never" and "almost never" was judged as 'absent'.

Statistical methods

Data are presented as mean ± SD. UWS and CH-SWS flow rates showed a skewed distribution and were logarithmically transformed ($\log^{10}$) before statistical analyses. For readability, the original (untransformed) data are presented in Table 3. Normally distributed data (DTI and XI score) and the logarithmically transformed data were analyzed with independent Students *t*-tests. Correlations between XI, DTI, IWG and the logarithmically transformed UWS flow rates

Table 3. Mean flow rate ± SD of the unstimulated (UWS) and chewing-stimulated salivary flow rate (CH-SWS)

		UWS mL/min (SD)	CH-SWS mL/min (SD)	n
Gender	Male	0.34 (0.23)[a]	1.19 (0.69)[a]	64
	Female	0.21 (0.21)	0.75 (0.64)	30
Age group	≤ 64 years	0.32 (0.25)	1.12 (0.73)	63
	> 64 years	0.25 (0.14)	0.92 (0.62)	31
Edentulous	No	0.31 (0.24)	1.10 (0.74)	71
	Yes	0.26 (0.13)	0.89 (0.54)	22
Diabetic	No	0.30 (0.22)	1.09 (0.71)	80
	Yes	0.30 (0.26)	0.81 (0.61)	13
Urine output	No	0.30 (0.23)	1.06 (0.77)	68
	Yes	0.30 (0.21)	1.04 (0.52)	26
Xerogenic medication	0	0.29 (0.19)	1.08 (0.68)	36
	1	0.32 (0.26)	1.04 (0.76)	32
	2	0.33 (0.26)	1.14 (0.69)	17
	≥ 3	0.25 (0.11)	0.90 (0.70)	8
Smoking status	Non-smoker	0.28 (0.22)	1.00 (0.69)	73
	Smoker	0.38 (0.24)	1.31 (0.77)	17
Alcohol consumption	No	0.28 (0.23)	1.09 (0.79)	52
	Yes	0.32 (0.22)	1.02 (0.60)	39
Time dialysis	≤ 24 months	0.31 (0.20)	1.19 (0.58)	34
	> 24 months	0.29 (0.24)	0.98 (0.76)	59

[a] $P < 0.01$.

were subjected to Pearson's product-moment correlation analysis. To further explore relationships between IWG and both thirst (DTI score) and xerostomia (XI score), partial correlation coefficients were calculated after controlling for XI and DTI, respectively.

The main dependent variables (IWG, DTI score, XI score, and salivary flow rates) were subjected to a univariate ANOVA with gender, age (≤ 64 year, > 65 year), alcohol use and smoking habits as factors. Potential interactions between these variables were explored using a full factorial model (two-way ANOVA). The statistical analysis was performed using the statistical software package SPSS (version 10.0, SPSS Inc., Chicago, IL, USA). All levels of significance were set at $P < 0.05$.

RESULTS

Patients demographics

The total sample of this study comprised of 94 HD patients (64 men: age 54.8 ± 15.5 years; 30 women: age 59.5 ± 18.7 years). The mean time of treatment with HD was 35.8 ± 31.0 months.

The causes of chronic renal failure in the study group were renal vascular disease due to hypertension (16.0%), polycystic kidneys adult type (11.7%), glomerulonephritis (10.6%), miscellaneous (22.3%) and unknown (39.4%). In total, thirteen patients suffered from diabetes mellitus (type 1 or 2) which was the cause of the chronic renal failure in five individuals.

The main categories of putatively xerogenic medication used by the HD patients were antihistamines (24.2%) and antihypertensives (21.1%). The IWG of the patients was 2.2 ± 1.3 kg. The average systolic and diastolic blood pressure were 146 ± 22 and 81 ± 13 mm Hg, respectively (Table 1). The mean normalized protein catabolic rate was 1.1 ± 0.2 g/kg/day and correlated significantly with IWG ($r = 0.291$, $P = 0.033$).

Saliva secretion

The mean salivary flow rates of UWS and CH-SWS were 0.30 ± 0.22 mL/min and 1.05 ± 0.70 mL/min, respectively. Normal values (0.25-0.50 mL/min) were reported in 34.2% of the patients, and hyposalivation (UWS ≤ 0.15 mL/min) was found in 36.2% of the cases.[28]

Stratified data of the salivary flow rates are presented in Table 3. Male patients had significantly higher salivary flow rates than females, both for UWS and CH-SWS ($P < 0.001$). No diurnal differences in secretion rates were observed between patients who were treated in the morning versus the afternoon (data not shown). No significant differences in UWS and CH-SWS were observed with regard to age, dental status (dentate v.s. edentulous), diabetics, urine output, alcohol consumption, smoking, or total time on dialysis. No significant association was observed between the number of putatively xerogenic medications used and the UWS flow rate ($r = -0.018$, $P = 0.914$).

Xerostomia (Xerostomia Inventory)

The mean XI score of the study population was 28.3 ± 9.1. Significant differences were observed with regard to gender, age and alcohol consumption (Table 4). Women had higher XI scores (31.6 ± 9.7) than men (26.7 ± 8.5; $P = 0.019$). Participants older than 65 years reported significant lower XI scores (23.1 ± 7.7) than subjects below the age of 65 years (31.4 ± 9.1; $P < 0.0005$). In 74.2% of the patients a subjective dry mouth was present. A small majority of the study population (52.3%) reported to have problems with eating dry food and 61.3% of the patients sipped liquids to aid in swallowing food.

The total number of all medications used was positively correlated with the XI score ($r = 0.257$, $P = 0.016$). However, no significant association was found between the number of putatively xerogenic medications used and the XI score ($r = 0.039$, $P = 0.717$). A large difference was observed between female patients who smoked (DTI score = 32.0 ± 4.2) and nonsmoking patients (21.3 ± 8.0). In contrast, no difference was observed between male smokers and nonsmokers.

Table 4. Mean XI score ± SD (xerostomia inventory) and DTI score ± SD (dialysis thirst inventory)

		XI score (SD) (range 11-55)	DTI score (SD) (range 7-35)	n
Gender	Male	26.7 (8.5)[a]	19.3 (6.6)	60
	Female	31.6 (9.7)	22.2 (8.4)	28
Age group	≤ 64 years	31.4 (9.1)[b]	22.2 (6.5)[b]	49
	> 64 years	23.1 (7.7)	16.7 (7.7)	23
Edentulous	No	29.1 (8.7)	21.0 (6.7)	65
	Yes	25.7 (10.1)	18.1 (9.0)	22
Diabetic	No	27.7 (8.6)	20.8 (7.7)	76
	Yes	31.5 (12.0)	20.2 (7.3)	12
Urine output	No	28.8 (9.1)	20.5 (7.3)	64
	Yes	26.8 (9.3)	19.8 (7.7)	24
Xerogenic medication	0	28.2 (8.5)	19.9 (7.2)	32
	1	28.5 (9.5)	21.3 (7.3)	32
	2	26.9 (9.5)	20.0 (8.5)	16
	≥ 3	28.6 (13.3)	18.7 (7.4)	7
Smoking status	Non-smoker	28.4 (8.8)	20.3 (7.2)	71
	Smoker	27.3 (10.8)	20.7 (8.5)	16
Alcohol consumption	No	30.0 (10.0)[a]	21.4 (7.8)	49
	Yes	25.9 (7.4)	18.8 (6.7)	38
Time dialysis	≤ 24 months	26.1 (8.3)	18.0 (7.4)	34
	> 24 months	29.6 (9.4)	21.6 (7.1)[a]	54

[a] $P < 0.05$; [b] $P < 0.01$.

Thirst (Dialysis Thirst Inventory)

The mean DTI score of the patients was 20.3 ± 7.3. Patients over the age of 65 years had significant lower DTI scores than subjects younger than 65 years (16.7 ± 7.7 and 22.2 ± 6.5, respectively; $P < 0.0005$), see Table 4. Patients > 24 months on dialysis reported more thirst (DTI score = 21.6 ± 7.1) than patients ≤ 24 months on dialysis (DTI score = 18.0 ± 7.4). Table 2 gives an overview of the scores for each item of the DTI. Of the patients, 39.1% reported thirst as a problem (fairly to very often). During daytime, 47.8% of the patients reported to have thirst. During the night the proportion of patients with thirst decreased to 29.3%. In 38.1% of the study group, social life is influenced by thirst. Before a dialysis session, the perceived thirst is much higher (41.6% 'fairly often' or 'very often') than during dialysis (24.7%) or afterwards (29.9%).

A nearly significant association was observed between the DTI score and the number of medications used ($r = 0.212$, $P = 0.065$). Significant two-way interactions for the DTI score were observed between gender and smoking [$F(1,65) = 4.63$, $P < 0.05$] and between age and alcohol [$F(1,65) = 5.91$, $P < 0.05$]. A large difference was found between female patients who

smoked (DTI score = 32.0 ± 4.2) and non-smoking patients (DTI score = 21.3 ± 8.0). In contrast, no difference was observed between male smokers and non-smokers.

Relationships between IWG, thirst, xerostomia, and saliva secretion

A strong positive correlation between thirst and xerostomia was found ($r = 0.736$, $P < 0.0005$; Figure 1). Thirst and xerostomia are associated with IWG, as shown by the significant correlations of both the XI score and DTI score with IWG ($r = 0.376$, $P = 0.001$ and $r = 0.250$, $P = 0.020$ respectively; Figure 2 and 3). Thirst was inversely and significantly correlated with the UWS flow rate ($r = -0.227$, $P = 0.049$). No significant correlation was observed between UWS flow rate and the IWG.

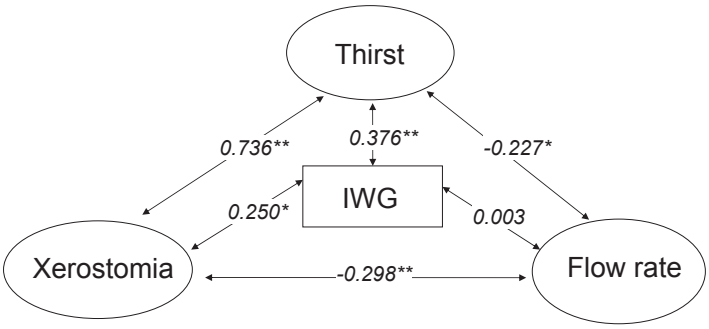

Figure 1. Pearson correlations, between xerostomia (XI score), thirst (DTI score) and flow rate (UWS) and interdialytic weight gain (IWG).
* $P < 0.05$, ** $P < 0.01$

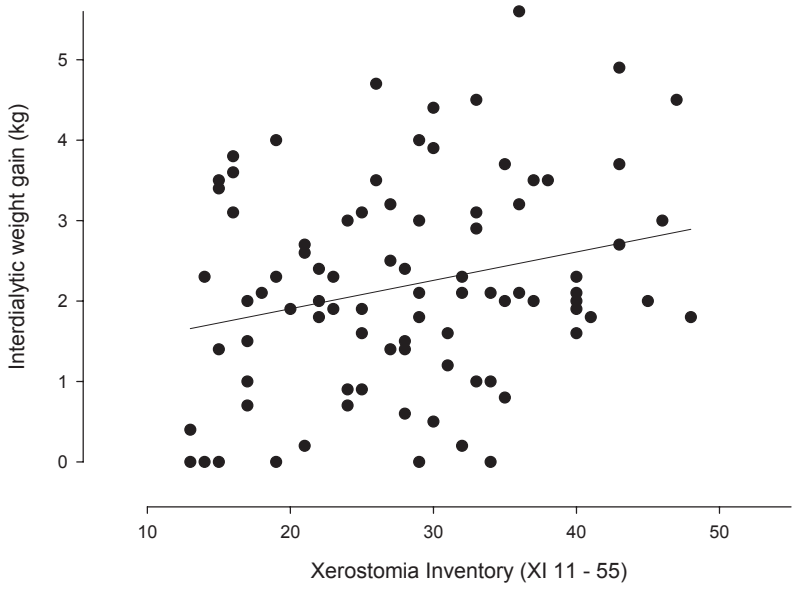

Figure 2. Relationship between interdialytic weight gain (IWG) and xerostomia inventory (XI). Pearson correlation ($r = 0.250$, $P < 0.05$)

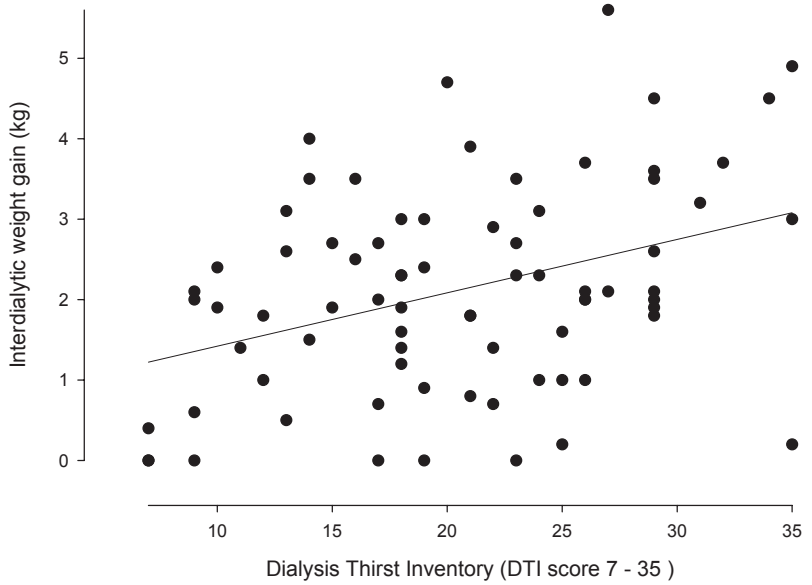

Figure 3. Relationship between interdialytic weight gain (IWG) and Dialysis Thirst Inventory (DTI). Pearson correlation ($r = 0.376$, $P < 0.005$)

Partial correlation coefficients between thirst and IWG remained significant after controlling for the XI score ($r = 0.253$, $P = 0.031$). After controlling for DTI score, the correlation between xerostomia and IWG was no longer significant ($r = 0.038$, $P > 0.05$). The correlation between DTI score and XI score remained high after controlling for IWG ($r = 0.700$, $P < 0.01$). No significant interactions of gender and age with smoking status and alcohol consumption were observed for IWG, thirst, xerostomia, or salivary flow rate.

DISCUSSION

The present study is the first large scale, multicenter study to investigate whether aspects of oral dryness, especially salivary flow rate and xerostomia, were related to thirst and IWG. We indeed found significant relationships between a dry mouth (both xerostomia and reduced salivary flow rates) and thirst, and xerostomia and IWG. This suggests a possible role of oral dryness to explain higher fluid intake between HD sessions, and opens future interventions to manipulate dry mouth and/or flow rates to decrease thirst and IWG in HD patients.

A subjective feeling of a dry mouth (xerostomia) in HD patients was assessed using a validated xerostomia questionnaire (XI) with high scores indicating severe complains of oral dryness. We found that the subjective dry mouth feelings of HD patients (XI = 28.3 ± 9.1) were similar to patients receiving radiotherapy for head- and neck cancer two months after the initial radiotherapy (XI = 31.4 ± 7.3).[29] A relatively large proportion of the HD patients in our study reported to have a dry mouth (76.4%). This is in agreement with previous studies on HD

patients, in which the percentage of patients reporting a dry mouth ranged between 32.9% and 66.7%.[17,18] Remarkably, no significant association was observed between the number of putatively xerogenic medications used and the XI score. The absence of this association may be either the result of the relatively broad classification of putatively xerogenic medication or the interaction between multiple medications used by HD patients.[31]

In our study, the mean XI score of HD patients over the age of 65 years (XI = 23.1 ± 7.7) is similar to reports of oral dryness in healthy subjects over 65 years (XI = 20.0 ± 7.0).[31] However, HD patients under the age of 65 years have much higher XI scores (31.4 ± 7.7), which might be explained by a gradual habituation to a dry mouth over the years. It has been suggested that younger subjects may also be more likely to experience symptoms of oral dryness when salivary flow is low, while in older persons symptoms of dry mouth could be related to a more complex constellation of factors where salivary flow is only one component.[32] A large scale epidemiological survey among an adult population, however, found a strong positive correlation between age and reports of a dry mouth.[33] Similarly, in our study, age and gender differences for the level of xerostomia (XI) and salivary flow rates (UWS and CH-SWS) in HD patients were observed. This is consistent with previous studies that men have higher salivary flow rates than women, and women report more xerostomia.[31,32,34,35]

The mean salivary flow rates of both unstimulated (UWS) and stimulated saliva (CH-SWS) in HD patients were normal and comparable to reference values for healthy subjects.[36] However, it should be mentioned that the original flow rate date were skewed to the right and had a large standard deviation. Many HD patients have low salivary flow rates. The calculated mean rates were normal due to a few HD patients with high flow rates. The mean UWS in our study was also consistent with the study of Galvada and co-workers, who found an average UWS flow rate of 0.26 ± 0.28 mL/min in HD patients compared to controls (UWS = 0.28 ± 0.16 mL/min).[16] Kho and co-workers investigated 22 patients undergoing HD and found an average UWS flow rate of 0.30 ± 0.18 mL/min.[17]

Our observation that the mean CH-SWS of HD patients was comparable to reference values for healthy subjects[36] differs from previous studies reporting that the stimulated salivary flow rates were significantly reduced in HD patients compared to control groups.[15,17,20,21] This could be explained by the fact that in our study a tasteless piece of parafilm was used to stimulate salivary flow, while previous studies used other mechanical or chemical stimuli like citric acid (2%). The altered taste perception of HD patients may also partially contribute to these different findings.[37]

The salivary flow rate (UWS) and the perception of a dry mouth (XI) correlated significantly (r = -0.298, $P < 0.05$), which is in agreement with previous studies reporting a correlation between objective measures of a dry mouth (salivary flow rate) and subjective reports of a dry mouth (xerostomia) in patients with rheumatoid arthritis.[38,39] Responses to questions related to eating (such as 'my mouth feels dry during eating a meal,' 'sipping liquids to aid swallowing,' and 'difficulties in swallowing dry food') were highly indicative of salivary performance.[40]

However, a subjective dry mouth is not always necessarily related to a reduced salivary flow rate[39-41] and other factors including anxiety, depression, and stress might play a role in the perception of a dry mouth.[35,42] It has been demonstrated that anxiety, depression and stress also play a role in the compliance of HD patients to fluid restriction, measured by the IWG.[4]

For this study a new Dialysis Thirst Inventory (DTI) was developed, focusing on perceived thirst. Significantly lower thirst scores were observed in the age group over 65 years, which is comparable to reduced complaints of oral dryness (XI) in the older aged HD patients. Our findings are also in agreement with diminished feelings of thirst and reduced fluid intake in healthy elderly persons.[43,44] Older subjects may have a higher osmotic operating point for thirst sensation, a diminished response by baroreceptors to volume changes or adaptation to the fluid restriction.[44]

Several investigators have suggested that the salivary glands are directly damaged by either uremic involvement or the fluid-restricted diet.[15-18,21] In the present study, the salivary flow rates are not influenced by the duration of HD treatment. This in agreement with the study of Bayraktar and co-workers in which no differences in salivary flow rate were observed between patients on HD for more or less than 24 months.[21] Also, the large difference between the unstimulated and stimulated flow rate in our study indicates that the salivary glands have maintained their secretory capacity. This all indicates that the salivary glands are probably not damaged by chronic HD treatment.

Because our study clearly demonstrates that thirst (DTI) and xerostomia (XI) are associated with greater IWG, management of thirst and xerostomia is potentially of clinical importance in the treatment of HD patients. Patients on daily HD were less thirsty and also showed less fluctuation in body fluid volume.[45] In addition, xerostomia can be reduced by either stimulation of the saliva secretion (mechanical, gustatory, or pharmacologic) or palliative care using mouthwashes or saliva substitutes.[46-49] In healthy subjects, gum chewing increases flow rate to 187% during the first minute of chewing[50] (see Appendix) and gum chewing can, especially in those with low salivary function, increase unstimulated flow rates, and might contribute to reduced levels of xerostomia.[51] Regular use of gum for two weeks resulted even in a long-term persistent increase in unstimulated salivary secretion rate and showed to be effective in reducing xerostomia.[52] Also, in patients with advanced cancer, daily use of chewing gum or a saliva substitute showed to be effective in reducing xerostomia.[48] Use of saliva substitutes reduced dry mouth feelings in patients with irradiation-induced xerostomia.[53] In a small pilot study, use of a saliva substitute in HD patients resulted in a reduction of fluid overload.[54]

CONCLUSION

The mean unstimulated and stimulated salivary flow rates of HD patients in this study are relatively normal. However, a large proportion of the patients have reduced unstimulated

flow rates. Thirst, IWG, and xerostomia are associated in HD patients, indicating a possible role of oral dryness to explain higher fluid intake between HD sessions. In other studies, the use of saliva stimuli or saliva substitutes showed to be effective in reducing feelings of a dry mouth. This might also diminish the urge to drink in HD patients, enhancing compliance to the fluid-restricted diet and leading to a decreased IWG and fewer systemic complications. The potential clinical effect of saliva stimuli and saliva substitutes will be investigated in Chapter 6 and 7.

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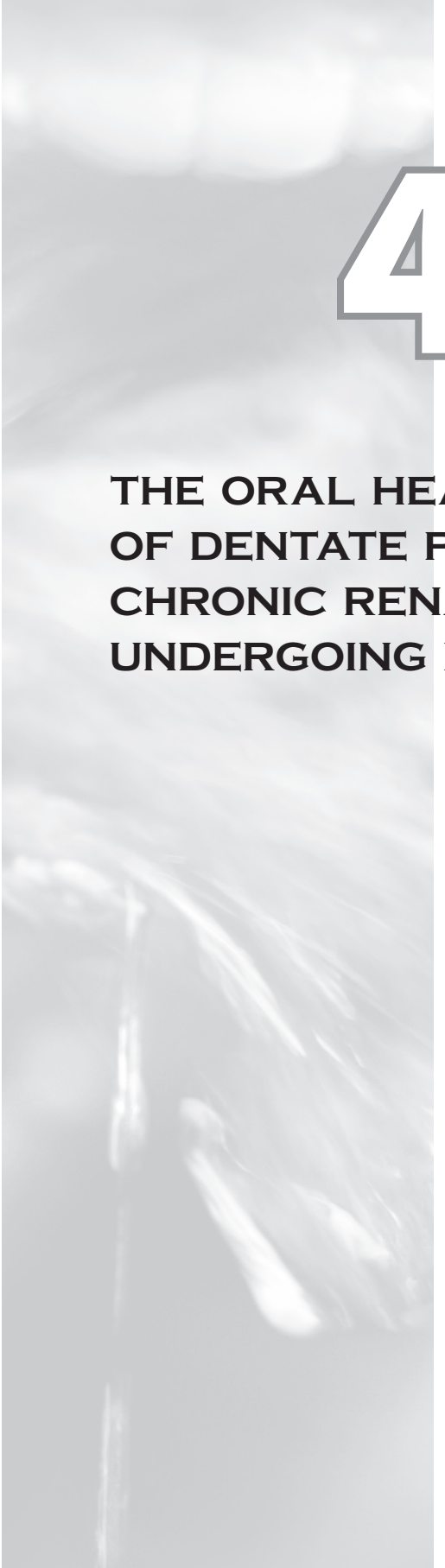

4

THE ORAL HEALTH STATUS OF DENTATE PATIENTS WITH CHRONIC RENAL FAILURE UNDERGOING DIALYSIS THERAPY

Casper P. Bots, Jan H.G. Poorterman, Henk S. Brand, Huib Kalsbeek, Barbara M. Van Amerongen, Enno C.I. Veerman, Arie V. Nieuw Amerongen

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ABSTRACT

Objective

The aim of this study was to compare the oral health status of chronic renal failure patients (CRF) on renal replacement therapy with a matched reference population.

Material and Methods

In a cross-sectional study, forty-two dentate CRF patients – aged 25-52 years old – were matched with a reference group of 808 dentate subjects. The oral health was assessed using decayed missing filled (DMF) indices, simplified oral hygiene index (SOHI) and periodontal status. An oral health questionnaire was used to assess self-reported dental problems. Students *t*-tests and chi-square tests were performed to compare the CRF patients with the controls.

Results

All index-scores in the CRF patients were comparable with the controls except for number of teeth covered with calculus that was significantly higher ($P < 0.05$) in CRF patients (4.1 ± 2.6) than in controls (3.0 ± 2.9). The self-reported oral health questionnaire revealed a trend for increased temporomandibular complaints in CRF patients (16.7% vs 5.7% in controls; $P = 0.06$) as well as bad taste (31.0% vs 6.8% in controls, $P = 0.08$)

Conclusion

For most dental aspects, the oral health of CRF patients is comparable with controls.

INTRODUCTION

The major function of the kidneys is removal of metabolic waste products, electrolytes and water. When this function is impaired towards 5-10% of the original capacity, end stage renal disease (ESRD) can lead rapidly to death, unless renal replacement therapy is started. Chronic dialysis therapies, such as hemodialysis (HD) and peritoneal dialysis (PD) have proven to be successful in replacing the major functions of the kidney. In HD treatment, an artificial extra-corporal device is used to clear the blood of waste products and excess fluid. Access to the circulatory system is obtained through a surgically created arteriovenous shunt, and anticoagulants are administered during dialysis. HD treatment must be performed every 2-3 days for 4-5 hours. In PD treatment, the patients' peritoneal membrane is used as an artificial kidney. Sterile dialysis fluid is introduced into the abdominal cavity for several hours, drained and refreshed several times during the day (Continuous Ambulatory Peritoneal Dialysis = CAPD) or continuously at night (Continuous Cycler-Assisted Peritoneal Dialysis = CCPD).

Both HD and PD treatment cause systemic changes, oral complications and alterations in salivary composition and output.[1,2] In addition, vomiting and reduced oral (self) care could also negatively affect the oral health in chronic dialysis patients resulting in more caries, periodontitis and oral lesions.[1,2,3] However, conflicting data exist on the effect of chronic dialysis therapy on oral health status.[4,5,6] Galvada and co-workers reported in a study with 53 HD patients, that the number of decayed missing and filled teeth (DMFT) and the level of periodontal attachment did not differ from a matched control group.[5] Increased salivary urea levels could induce calculus formation, but on the contrary also contribute to the remineralization of dental enamel, leading towards a lower caries experience in children.[7] No differences were found for the caries variables between adult HD patients and controls.[8] On the contrary, another study reported that the prevalence of periodontitis and caries experience was high in dialysis patients, but this study lacked a control group.[4]

Therefore, the aim of this cross-sectional study was to compare the oral health status of chronic renal failure (CRF) patients on renal replacement therapy with a matched reference population.

MATERIAL AND METHODS

Patients

The CRF patients undergoing kidney replacement therapy for at least three months were asked to participate. One hundred twenty six dialysis patients (HD, n = 95 ; (C)APD, n = 31) gave informed consent to participate in this study, which was approved by the Medical Ethical Committee of the Vrije Universiteit Medical Center, Amsterdam, The Netherlands. Twenty-nine patients (23.0%) were edentulous and 13 participants (10%) were physically not able to

participate in the clinical dental investigation. This resulted in 84 dentate CRF patients available for matching with a control group of 808 dentate subjects from a dental epidemiological study among subjects aged 25-54 years old.[9] The CRF patients were matched with the control group with regard to age [excluded < 25 years (n = 3) ; > 54 years (n = 39)] and educational level. Finally, this resulted in 42 dentate patients aged 25-54 years old, who matched with the reference group.

Age, gender and level of education were assessed with a questionnaire and the clinical data were retrieved from patient files. The main pathologies causing CRF, classified according to the European Dialysis and Transplantation Association- European Renal Association,[10] were IgA nephropathy (9.5%), glomerulonephritis (9.5%), polycystic kidney disease -adult type- (7.1%) and renal vascular diseases (7.1%).

Oral health assessment

The oral health assessment of the dialysis patients took place at a dental clinic nearby one of the dialysis centers. Two dentists examined each patient, subsequently. One dentist (JP) was involved in the assessment of both the oral health in the ESRD patients and the Dutch epidemiological caries study, which was carried out in the same year (2002). The data presented are based on the consensus reached after the two inspections. The intraclass correlation coefficient for the DMFT and plaque index was 0.99 and 0.86 respectively, indicating good intratest reliability for these variables.[11]

The teeth were dried with air and inspected with a standard dental mirror and assessed according to the same protocol as used in the reference group.[9] This protocol consists of several generally accepted oral health indices, such as the DMFT and DMFS, in addition the amount of dental plaque was assessed.[12,13,14] The periodontal status including pocket depth, bleeding on probing (none, minor, moderate and on probing) and presence of calculus was assessed using a split mouth model (1^{st} – 3^{rd} quadrant or 2^{nd} – 4^{th} quadrant), to which the patients were randomly allocated. A questionnaire was used to assess specific dental issues such as problems with 'caries', 'gingiva', 'jaw pain', 'ulcerations', 'bad breath' or 'pain', during the preceding year.

Statistical methods

Data are presented as percentages, mean ± SD and the 95% confidence interval (CI) of the mean difference. The means of quantitative oral health data from the dialysis patients were compared with the matched reference population using independent Student *t*-tests, chi-square tests or Fisher's exact tests when appropriate. All levels of significance were set at $P < 0.05$.

RESULTS

After matching by age and educational level with a control group of 808 patients (326 men and 482 women; mean age 41.3 ± 8.4 years) from a dental epidemiological study, the total sample of CRF patients comprised 42 patients (30 men and 12 women; mean age 42.6 ± 9.2 years). Twenty-eight CRF patients were on HD, eight on CAPD and six on CCPD, see Table 1.

Seven percent had one or more bridges in the maxilla and/or mandible. The amount of CRF patients' wearing a partial denture in the maxilla was comparable with the control group (data not shown). Table 2 shows the data regarding the DMF indices. Both the DMFT and DMFS scores were comparable in CRF patients (DMFT = 13.3 ± 7.5; DMFS = 37.2 ± 23.7) and controls (DMFT = 14.7 ± 6.4; DMFS = 39.1 ± 22.0). No statistically significant differences were observed for any of the DMF-indices.

Both CRF patients and matched controls had the same amount of surfaces covered with dental plaque (2.4 ± 1.6 vs 2.6 ± 1.4, respectively), see Table 3. CRF patients had significantly more teeth covered with calculus (4.1 ± 2.6) than controls (3.0 ± 2.9; $P < 0.05$). The percentage

Table 1. Clinical and demographical data of patients with chronic renal failure (CRF) on dialysis (n = 42)

Age (years)			42.6 (9.2)	
Male gender (%)			71.4%	(n = 30)
Educational level	*Primary school*		33.3%	(n = 14)
	Secondary school		35.7%	(n = 15)
	High school or higher		31.0%	(n = 13)
Months on dialysis			28.6 (16.9)	
Therapy	*Hemodialysis*		66.7%	(n = 28)
	Peritoneal dialysis:	*CAPD*	19.0%	(n = 8)
		CCPD	14.3%	(n = 6)

Percentages and numbers of clinical and demographic variables. Mean values (SD) are given for continuous variables.
Abbreveations: CAPD, continues ambulatory peritoneal dialysis; CCPD, continues cycler-assisted peritoneal dialysis

Table 2. Decayed Missing Filled index values (mean ± SD) of patients with chronic renal failure (CRF) on dialysis compared to a matched reference group

	CRF (n = 42)	Controls (n = 808)	95% CI mean difference
Decayed Teeth (DT)	1.4 (1.9)	1.3 (1.8)	-0.5 – 0.7
Missing Teeth (MT)	3.7 (5.2)	3.7 (5.6)	-1.8 – 1.8
Filled Teeth (FT)	8.1 (5.8)	9.7 (5.6)	-0.2 – 3.4
Decayed Missing Filled Teeth (DMFT)	13.3 (7.5)	14.7 (6.4)	-0.6 – 3.4
Decayed Surfaces (DS)	1.6 (2.6)	1.6 (2.9)	-0.9 – 0.9
Missing Surfaces (MS)	14.3 (18.7)	14.3 (20.1)	-6.3 – 6.3
Filled Surfaces (FS)	21.3 (16.5)	23.3 (16.3)	-3.1 – 7.1
Decayed Missing Filled Surfaces (DMFS)	37.2 (23.7)	39.1 (22.0)	-5.0 – 8.8

No significant differences were found between the two groups

Table 3. Dental plaque, calculus and periodontal health in patients with chronic renal failure (CRF) on dialysis compared to a matched reference group

		CRF (n = 42)	Control (n = 808)	*P*
Dental plaque (> 2 teeth assessed)				
Number of surfaces assessed		5.4 ± 1.0	5.7 ± 0.8	n.s.
Number of surfaces with dental plaque		2.4 ± 1.6	2.5 ± 1.4	n.s.
Score dental plaque (% surfaces):	0	54.1%	56.3%	n.s.
	1	32.6%	31.6%	n.s.
	2 , 3	13.3%	12.2%	n.s.
Calculus (> 4 teeth assessed)				
Number of teeth assessed		12.3 ± 2.1	12.2 ± 2.2	n.s.
Number of teeth *with* calculus		4.1 ± 2.6	3.0 ± 2.9	$P < 0.05$
Calculus (% teeth):	no	65.6%	75.4%	n.s.
	supra or subgingival	34.4%	24.6%	n.s.
Pockets (> 4 teeth assessed)				
Number of teeth assessed		12.3 ± 2.1	12.2 ± 2.2	n.s.
Number of teeth *with* pocket (≥ 4mm)		1.8 ± 2.0	1.6 ± 2.3	n.s.
Pockets (% teeth):	≤ 3.5 mm	95.8%	86.9%	n.s.
	> 3.5 and ≤ 5.5mm	3.3%	11.5%	n.s.
	> 5.5 mm	1.0%	1.6%	n.s.
Bleeding on probing (> 4 teeth assessed)				
Number of teeth assessed		11.6 ± 3.3	12.2 ± 2.2	n.s.
Number of teeth *with* bleeding		2.8 ± 2.2	3.0 ± 3.0	n.s.
Bleeding (% teeth):	no bleeding	62.1%	66.0%	n.s.
	minor	12.4%	9.4%	n.s.
	moderate	1.9%	16.4%	n.s.
	immediately on probing	21.2%	8.2%	n.s.

Students *t*-tests and chi-square tests were performed, n.s.= no statistical significant difference.

of supra- and subgingival calculus was slightly higher in CRF patients (34.4%) than in controls (24.6%). A statistically significant association was found between the number of teeth covered with dental plaque or calculus and the number of elements with bleeding on probing ($r = 0.543$; $P < 0.001$ and $r = 0.568$; $P < 0.001$, respectively).

The periodontal pocket status did not differ between CRF patients and controls. Also, the total number of elements with bleeding on probing did not differ. Although the percentage of teeth bleeding immediately after probing in CRF patients was higher (21.2%) than in controls (8.2%), and no statistically significant differences were observed. The majority of the CRF patients (97.6%) brushed daily (28.6% once a day, 64.3% twice a day, 19.0% more than twice a day) which does not differ from of the controls (96.6% brushing daily). During the preceding year, 81% of the CRF patients (n = 34) had received professional oral care at least once, which is comparable with the reference group.

Table 4. Self-reported oral health during the preceding year in CRF patients on dialysis compared with healthy controls

	CRF (n = 42)		Controls (n = 808)		*P*
Caries lesions	41%	(n = 17)	25%	(n = 203)	*0.25*
Gingival problems	36%	(n = 15)	28%	(n = 226)	*0.28*
Temporomandibular complaints	17%	(n = 7)	6%	(n = 46)	*0.06*
Ulcerations	21%	(n = 9)	12%	(n = 95)	*0.12*
Problems with eating and drinking	10%	(n = 4)	21%	(n = 172)	*0.19*
Missing, moving or broken teeth	17%	(n = 7)	21%	(n = 166)	*0.21*
Distortion of teeth position	7%	(n = 3)	11%	(n = 88)	*0.11*
Bad breath	24%	(n = 10)	12%	(n = 96)	*0.12*
Sharp edges of the teeth	24%	(n = 10)	14%	(n = 111)	*0.14*
Bad taste	31%	(n = 13)	7%	(n = 55)	*0.08*
Discolouration of the teeth	21%	(n = 9)	26%	(n = 211)	*0.26*
Pain	14%	(n = 6)	15%	(n = 118)	*0.15*

Chi-square or Fisher's exact tests were performed. No significant differences were found

The association between duration of hemo- or peritoneal dialysis and the various oral health variables was investigated, however, no significant associations were found for any of these variables.

The self-reported oral health questionnaire revealed that CRF patients did not differ from the control group, see Table 4. However, trends were observed for the increased frequency of temporomandibular complaints in CRF patients (16.7% vs 5.7% in controls; $P = 0.06$) and bad taste (31.0% vs 6.8% in controls; $P = 0.08$).

DISCUSSION

In this study, the oral health of 42 dentate CRF patients was assessed and compared to a matched reference group of 808 healthy subjects. The DMFT and DMFS scores tended to be higher in the control group than in the patient group, but the difference was not statistically significant. These observations are in accordance with previous studies.[4,5,6] Galvada and co-workers also found no statistically significant difference between the number of carious, absent and obturated teeth (CAO) in 105 renal patients on HD treatment (CAO = 14.9 ± 8.7) compared to 53 gender matched controls (13.3 ± 7.9).[5]

It has been suggested by others that the caries activity in patients on dialysis is lower, as an increased urea concentration in saliva leads to higher pH levels.[1,15] Higher salivary urea levels could potentially protect the teeth from demineralisation but on the other hand enhance calculus formation in dialysis patients.[16] The higher prevalence of calculus we found, suggest that CRF patients received less oral care. This seems not feasible, since almost every participant had visited an oral healthcare worker during the preceding year. It should be taken into

account that in general, almost everyone (86%) in The Netherlands visits the dentist once or twice a year.[9]

It might be possible that the effect of a relatively short period of dialysis treatment (28.6 ± 16.9 months) may not be reflected in the DMFT index, which is a measure for the life-long caries experience. Long-term dialysis treatment might affect the carious component of the DMFT,[7,16,17] although studies focusing on the duration of dialysis treatment in relation to oral health did not show a substantial effect.[4,6]

Our results potentially could have been biased as only relatively healthy and mobile CRF patients were able to participate in this study, thus missing those in a very poor physical condition.

We found that the number of teeth with calculus was significantly higher in the patient group than in controls. This is in accordance with the study by Galvada and co-workers who found a significantly higher calculus index in HD patients compared to controls.[5] However, in contrast to their study, we found no differences between CRF patients and controls with respect to the amount of dental plaque. Since in our study the frequency of dental hygiene procedures and dental plaque levels were comparable in both groups, it seems feasible that other factors such as salivary changes might have contributed to higher calculus deposition.

A strong correlation between the number of teeth with bleeding and the number of teeth covered with dental plaque and calculus was found. This is in agreement with previous studies on healthy individuals.[18,19] An improvement in oral hygiene might reduce the amount of dental plaque and calculus, resulting in a reduction of the number of elements with bleeding. However, it should be taken into account that medication of HD patients, such as anticoagulant therapy, might mask the effect of an improvement of oral health measures. We found support of this concept in our data since the increased prevalence of calculus and the higher number of bleeding on probing was not reflected in the severity and number of pocket depths (Table 3). This finding also indicates that the increased bleeding on probing does not directly reflect the level of inflammation (gingivitis or periodontitis) in CRF patients, which is in accordance with findings from Marakoglu and co-workers.[6]

In our study, the data of the self-reported oral health questionnaire suggested a trend towards an increase of taste disturbances in CRF patients.[20-23] Thirty one percent of the CRF patients in our study reported to have had a bad taste, in the preceding year. This is in accordance with another study that showed that 31.7% of HD patients had taste changes.[24] These taste disturbances could be caused by metabolic disturbances, the use of medication, a diminished number of taste buds and changes in salivary flow rate and composition.[1,21,22,25]

Also, the number of temporomandibular complaints showed a tendency to be higher in CRF patients than in the control group. This finding might be related to renal osteodystrophy, caused by increased parathyroid functions associated with inappropriate vitamin D, calcium and phosphorus metabolism in dialysis patients.[26,27]

CONCLUSION

We have shown that most dental aspects of oral health in CRF patients are comparable to a well-matched control group. In CRF patients, the number of teeth covered with calculus was significantly higher. However, many CRF patients are candidates for renal transplantation and need to be kept foci free. Therefore, maintaining good oral health is of major importance since oral pathologies or infections could jeopardize the opportunity to receive a successful kidney transplant.[28]

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5

ORAL AND SALIVARY CHANGES IN PATIENTS WITH END STAGE RENAL DISEASE: A TWO-YEAR FOLLOW-UP STUDY

Casper P. Bots, Henk S. Brand, Jan H.G. Poorterman, Barbara M. van Amerongen, Marianne Valentijn-Benz, Enno C.I. Veerman, Piet M. ter Wee, Arie V. Nieuw Amerongen

Submitted

ABSTRACT

Objectives

To compare oral health, salivary flow rate, xerostomia and thirst in end stage renal disease (ESRD) patients remaining on dialysis treatment and after renal transplantation.

Material and methods

ESRD patients from dialysis centers in Amsterdam, The Hague and Utrecht, The Netherlands were included in a longitudinal observational study. At baseline and after two years, salivary flow rates, xerostomia and thirst were determined in 43 ESRD patients. The number of decayed missing filled teeth/surfaces (DMFT/DMFS) was recorded, and periodontal status assessed.

Results

After renal transplantation (n = 20), the salivary flow rate increased significantly from UWS = 0.30 ± 0.21 mL/min to 0.44 ± 0.29 mL/min ($P < 0.001$) and the level of xerostomia and thirst decreased. After two years, the percentage of bleeding on probing in dialysis patients (n = 23) decreased from 29.5 ± 25.4 till 10.3 ± 12.3 percent, ($P < 0.050$) further oral health differences were found between dialysis and renal transplant patients.

Conclusion

DMFT, dental plaque, gingival bleeding and periodontal indices did not change remarkable after two years, comparing dialysis and renal transplant patients. Increased salivary flow rates, decreased xerostomia and thirst in renal transplant patients are important aspects in the quality of life of these patients.

INTRODUCTION

Over the last decades, the prevalence and incidence of patients with end stage renal disease (ESRD) has increased.[1] Due to improvements in medical care and prolonged life expectancy, patients with renal disorders are increasingly encountered in the dental practice.[2]

A broad variety of oral manifestations has been reported in ESRD patients including gingivitis, xerostomia, ammonia-like smell, mucosal pallor and lesions, tooth mobility, malocclusion and an increased risk for dental erosion due to frequent regurgitation.[3-7] Systemic and salivary changes due to chronic renal failure, the use of multiple medication, vomiting and reduced oral self care could all potentially affect the oral health in these patients.[8;9]

The kidneys are essential to remove metabolic waste products, electrolytes and water. When the function of the kidneys is impaired towards 5-10% of the original capacity ESRD occurs, requiring either hemodialysis (HD) or peritoneal dialysis treatment (PD) or renal transplantation (NTx). In HD, an extra-corporal device is used, whereas in PD the peritoneal membrane acts as a filter. NTx patients receive their allograft from living or cadaveric donors. To prevent allograft rejection, immunosuppressant therapy is required including the use of prednisolone, cyclosporine or tacrolimus, which could also affect the oral health.[4]

Relatively little is known about the long-term effects of dialysis treatment on oral health. In addition, most studies on the oral health and salivary flow rate in transplantation patients have had a cross-sectional set-up, comparing different renal replacement therapies with healthy controls.[7;10;11]

Therefore, the aim of this study was to longitudinally compare oral health, salivary flow rate, xerostomia and thirst in dialysis patients with those ESRD patients who were transplanted during this period.

MATERIALS AND METHODS

Participants

ESRD patients undergoing renal replacement therapy for at least three months were asked to participate in a longitudinal study to assess thirst, oral dryness and oral health. One hundred twenty six dialysis patients (HD, n = 95; (C)APD, n = 31) gave informed consent to participate in this study. Excluded were 29 patients (23%) because they were edentulous, in addition thirteen participants (10%) were physically not able to participate in the clinical dental investigation. This resulted in 84 patients that were enrolled in this study, which was approved by the Medical Ethical Committee of the Vrije Universiteit Medical Center, Amsterdam, The Netherlands. However, 26 patients died during the two-year study period and fifteen subjects were lost to follow up or withdrew, see Figure 1. After two years, the data of in total 43 dentate ESRD patients were available for analysis.

Saliva, xerostomia and thirst

Unstimulated whole saliva (UWS) was collected according to the spitting method[12] with small modifications, as described previously.[13;14] All subjects were instructed to refrain from smoking, eating, drinking and tooth brushing for one hour prior to the three saliva collection periods. Before collection, the mouth was rinsed with tap water. The collection started with the instruction to void the mouth of saliva by swallowing. Subsequently, saliva was allowed to accumulate on the floor of the mouth and the subjects were instructed to spit out into the pre-weighed test tubes every 30 seconds. Each saliva collection period was five minutes.

Chewing stimulated whole saliva (CH-SWS) was also collected for five minutes using a flat piece of parafilm (5 x 5 cm; 0.30 g; Parafilm "M", American National CAL, Chicago, USA). During the saliva collection period, the subjects chewed at their own natural pace and stimulated saliva was collected in the same way as the unstimulated samples. The volume of saliva was determined gravimetrically (assuming 1 g = 1 mL) and the pH was determined within five minutes after saliva collection (Sentron pH-system 1001, Roden, The Netherlands).

A validated xerostomia inventory (XI) was used to quantify the level of xerostomia and consisted of 11 items, each with a five point Likert-type scale (never = 1 to very often = 5). Examples of the XI are e.g "My mouth feels dry", "My lips feel dry" and "I sip liquids to aid in swallowing food". The summed scores provide an individual XI score ranging from 11 (no dry mouth) to 55 (extremely dry mouth).[14;15]

The short-version of the Dialysis Thirst Inventory (DTI) was used to assess the level of thirst. The DTI questionnaire has four items, each with a five point Likert-type scale (never = 1 to very often = 5) providing a DTI score from 4 (no thirst) to 20 (extremely thirsty). The DTI questions are: " Thirst is a problem for me", " I am thirsty during the day", " I am thirsty during the night", and "My social life is influenced because of my thirst feelings",[16] see Chapter 6.

Oral health assessment

The oral health of the dialysis patients was measured independently by two dentists at a dental office nearby one of the dialysis centers, as described in chapter 4.[17] The teeth were dried

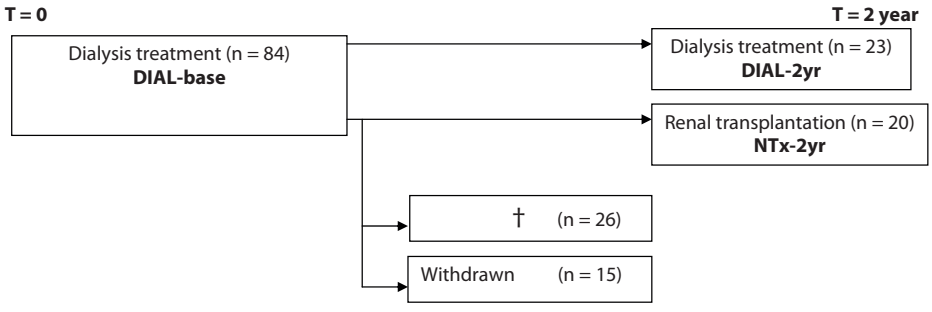

Figure 1. Flow chart of the longitudinal study on oral health in chronic renal failure patients during two years

with air and inspected with a standard dental mirror and oral health was determined with several generally accepted oral health indices, such as the decayed, missing, filled teeth index (DMFT), the decayed, missing, filled surfaces index (DMFS) and the Simplified Oral Hygiene Index (SOHI).[18-20] In addition, the periodontal status (bleeding on probing and pocket depth) was assessed using a split mouth model.

Statistical methods

All data are presented as means ± SD. UWS and CH-SWS flow rates showed a skewed distribution and were logarithmically transformed (log^{10}) before statistical analyses. For readability, the original (untransformed) data are presented in Table 1. The patients who remained on dialysis treatment (DIAL-2yr) were compared with those who had received a kidney transplant (NTx-2yr). Values of dialysis patients at baseline (DAIL-base) and after two years (DIAL-2yr), and those who were transplanted (NTx-2yr) were compared with Students *t*-tests. To explore the effects of each treatment modality (DIAL-2yr and NTx-2yr) on the main outcome variables, a general linear model of ANOVA (repeated measures design, followed by paired *t*-tests as post-hoc procedure) was performed. The statistical analysis was performed using the statistical software package SPSS (version 10.0; SPSS Inc., Chicago, IL. USA). Levels of significance were set at $P < 0.05$ and $P < 0.001$.

Table 1.

	Dialysis treatment	
	DIAL-base	**DIAL-2 yr**
UWS (mL/min)	0.31 (.19)	0.31 (.18)
CH-SWS (mL/min)	1.18 (.80)	1.09 (.54)
UWS (pH)	7.28 (.52)	7.10 (.71)
SWS (pH)	7.44 (.43)	7.28 (.57)
XI (11-55)	29.5 (7.5)^{y}	29.0 (9.5)^{x}
DTI_{sv} (4-20)	11.3 (3.8)	11.5 (4.0)^{x}
	Renal transplantation	
	DIAL-base	**NTx-2 yr**
UWS (mL/min)	0.30 (.21)	0.44 (.29)^{b}
CH-SWS (mL/min)	1.12 (.66)	1.38 (.84)
UWS (pH)	7.36 (.49)	6.74 (.40)^{a}
SWS (pH)	7.39 (.42)	7.00 (.24)^{a}
XI (11-55)	24.9 (8.1)	21.4 (7.6)
DTI_{sv} (4-20)	10.6 (4.4)	8.1 (2.6)^{b}

Data at baseline and after two-year follow up of dialysis patients who remained on dialysis (n = 23) and those who were transplanted (NTx; n = 20).

Comparison baseline and after two years is indicated as $^{a} = P < 0.001$; $^{b} = P < 0.050$, significant differences between those remaining on dialysis and those who were transplanted in the vertical row is indicated as $^{x} = P < 0.001$; $^{y} = P < 0.050$

RESULTS

Participants

In total 43 chronic dialysis patients participated in this study, 30 men (mean age 54.0 ± 15.7 years) and 13 women (mean age 48.9 ± 17.2 years). At baseline, the mean time on dialysis was 33.0 ± 28.6 months. The main pathologies causing ESRD, classified according to the European Dialysis and Transplantation Association-European Renal Association,[21] were polycystic kidney disease – adult type – (14.0%), IgA nephropathy (11.6%), glomerulonephritis (7.0%), miscellaneous (27.9%) and unknown (39.5%). After the two-year study period, 20 patients were transplanted on average 13.5 ± 7.1 months before the second measurement took place. Two NTx patients developed gingival overgrowth after renal transplantation, see illustration 1. In total 23 patients maintained on dialysis treatment, awaiting a renal transplant.

Illustration 1. Gingival overgrowth after the use of the use of cyclosporine

Saliva, xerostomia and thirst

The salivary flow rate of patients after renal transplantation (NTx-2yr) increased significantly from UWS = 0.30 ± 0.21 mL/min at baseline till UWS = 0.44 ± 0.29 mL/min after renal transplantation ($P = 0.002$), see Table 1. In the same patients, the salivary pH of UWS decreased from pH = 7.36 ± 0.49 till 6.74 ± 0.40 ($P < 0.001$) A same pattern was observed for CH-SWS. In patients who remained on dialysis during the study, the salivary flow rate of both UWS and CH-SWS was not altered.

At baseline, the XI values in those who remained on dialysis were higher (XI = 29.5 ± 7.5) than those who would receive a renal transplant (XI = 24.9 ± 7.5; $P < 0.05$), see Table 1. No other baseline differences were observed. In NTx patients, the XI scores decreased from 24.9 ± 8.1 till 21.4 ± 7.6, after two years ($P = 0.065$). No changes were observed for the XI scores after two years follow up, in patients who remained on dialysis. Also thirst in NTx patients

decreased significantly from DTI = 10.6 ± 4.4 till DTI = 8.1 ± 2.6, ($P = 0.020$). In patients maintaining on dialysis, no changes occurred and the DTI score remained high, see Table 1.

Oral health

Although the average DMFS and DMFT values slightly increased after two years, no statistically significant differences were observed between NTx and dialysis patients (see Table 2). In those patients who remained on dialysis, an increase in the number of missing surfaces (MS) was found from MS = 18.5 ± 2.9 to MS = 20.6 ± 25.6, after 2 year ($P = 0.017$). Subsequently, the DMFS value of these patients increased significantly, see Table 2.

In both groups, the percentage of teeth without dental plaque remained stable throughout the study (Table 3). The average percentage of explored sites that showed immediate bleeding on probing decreased significantly from 29.5 ± 25.4 till 10.3 ± 12.3 percent in patients continuing dialysis treatment. Also, in NTx patients, the percentage bleeding on probing decreased with 10%, although no statistically significant difference was found. In addition, no differences were found between NTx patients and those who remained on dialysis with respect to the pocket depth and bleeding measurements.

Table 2. Data at baseline and after two-year follow up of dialysis patients who remained on dialysis (n = 23) and those who were transplanted (NTx ; n = 20)

	Dialysis treatment	
	DIAL-base	**DIAL-2 yr**
Decayed Teeth (DT)	1.4 (2.1)	2.1 (3.5)
Missing Teeth (MT)	5.2 (6.9)	5.6 (7.5)
Filled Teeth (FT)	7.1 (6.1)	6.8 (6.3)
Decayed Missing Filled Teeth (DMFT)	13.6 (8.5)	14.4 (8.8)
Decayed Surfaces (DS)	1.8 (2.9)	2.9 (5.8)
Missing Surfaces (MS)	18.5 (23.6)	20.6 (25.6)*
Filled Surfaces (FS)	18.8 (18.5)	18.4 (18.8)
Decayed Missing Filled Surfaces (DMFS)	39.1 (26.9)	41.6 (27.8)*
	Renal transplantation	
	DIAL-base	**NTx-2 yr**
Decayed Teeth (DT)	1.5 (1.6)	2.1 (2.5)
Missing Teeth (MT)	3.3 (4.2)	3.6 (5.0)
Filled Teeth (FT)	10.0 (5.5)	9.6 (5.0)
Decayed Missing Filled Teeth (DMFT)	14.9 (8.1)	15.5 (7.8)
Decayed Surfaces (DS)	1.6 (1.9)	2.4 (2.7)
Missing Surfaces (MS)	12.3 (14.5)	13.8 (16.9)
Filled Surfaces (FS)	27.2 (17.6)	26.9 (17.0)
Decayed Missing Filled Surfaces (DMFS)	41.9 (26.6)	43.1 (25.3)

Comparison between baseline and after two years is indicated as * = $P < 0.050$. No significant differences between those remaining on dialysis and those who were transplanted (vertical row) were found at baseline or after two years.

Table 3. Data at baseline and after two-year follow up of dialysis patients who remained on dialysis (n = 23) and those who were transplanted (NTx; n = 20)

		Dialysis treatment	
		DIAL-base	**DIAL-2 yr**
Dental plaque (% surfaces)	0	49.7 (32.0)	49.9 (33.4)
	1	27.3 (25.0)	35.9 (30.2)
	2,3	18.5 (28.9)	9.6 (15.5)
Bleeding on probing (% teeth)	No bleeding	52.8 (29.0)	61.5 (32.4)
	Minor	14.9 (16.7)	11.8 (12.6)
	Moderate	2.8 (4.4)	2.8 (5.8)
	Immediately on probing	29.5 (25.4)	10.3 (12.3)*
Pocketdepth (% teeth)	≤ 3.5 mm	94.3 (7.4)	85.7 (29.5)
	> 3.5 – 5.5 mm	3.2 (4.6)	1.9 (3.4)
	> 5.5 mm	2.5 (6.0)	3.3 (9.3)
		Renal transplantation	
		DIAL-base	**NTx-2 yr**
Dental plaque (% surfaces)	0	52.4 (33.0)	62.6 (31.3)
	1	30.7 (25.8)	23.8 (24.5)
	2,3	16.9 (22.2)	13.6 (28.8)
Bleeding on probing (% teeth)	No bleeding	57.4 (26.2)	61.5 (38.9)
	Minor	11.8 (9.8)	7.2 (11.2)
	Moderate	2.0 (2.5)	6.2 (12.0)
	Immediately on probing	28.8 (19.2)	19.5 (32.7)
Pocketdepth (% teeth)	≤ 3.5 mm	96.4 (3.2)	96.9 (7.1)
	> 3.5 – 5.5 mm	3.2 (3.3)	2.8 (6.5)
	> 5.5 mm	0.4 (1.0)	0.1 (.6)

Comparison baseline and after two years is indicated as * = $P < 0.050$. No significant differences between those remaining on dialysis and those who were transplanted (vertical row) were found at baseline or after two years.

DISCUSSION

To our knowledge, this is the first longitudinal study to compare the course and changes in salivary flow rate, xerostomia, thirst and oral health of patients who remained on dialysis treatment, with those who received a renal transplant (NTx). It was revealed that oral dryness and thirst decreased after renal transplantation. In patients who remained on dialysis, the salivary variables and levels of xerostomia and thirst remained the same throughout the two-year study period. This indicates that thirst and oral dryness is a continuing problem in these patients. In dialysis patients, a significant increase in the number of MS and DMFS, and a reduction of bleeding on probing was found after the two-year observation period.

It was found that the salivary flow rates (both UWS and CH-SWS) increased in the NTx-patients, while remaining the same in patients on dialysis. Other studies have shown reduced salivary flow rates in HD patients compared to healthy controls.[7;22-24] Our observation that the

salivary flow rates increase after renal transplantation does not support the suggestion that dialysis treatment affects the salivary glands.[25] In the present study, we have shown that the reduced salivary flow rates are reversible and restore after transplantation. The salivary flow rates in NTx patients might even been underestimated since several studies have indicated that long term use of immunosuppressant therapy such as cyclosporine A could suppress the salivary flow rate.[26;27]

A decrease in salivary pH after transplantation is probably due to the reduced concentration of urea in saliva which can be hydrolyzed by oral bacteria into ammonia (with a relatively high pH).[28] A high salivary pH and buffering capacity in dialysis patients could potentially enhance remineralization although we could not demonstrate this effect in the present study.[29-32]

As initially expected, we have found decreased oral dryness and thirst in patients after renal transplantation. After renal transplantation, the physiological function of the kidney should restore, which normalizes serum composition, fluid balance, thirst and xerostomia. In Chapter 3, we have demonstrated in hemodialysis patients, that salivary flow rate and xerostomia are significantly correlated.[14] Therefore, an increase of UWS salivary flow rate after renal transplantation could explain a decreased level of xerostomia.[33]

The number of MS increased in those who remained on dialysis therapy, and no changes occurred in the transplantation group after two years. This might be explained since most patients awaiting a renal transplant have to undergo an oral examination to become foci free, which is part of the preoperative evaluation.[6] In addition, previously we have also found no differences for the DMFS, DMFT and periodontal indices between ESRD patients and a matched (age and educational status) control group (chapter 4).[17] In two patients, markedly increased gingival overgrowth was found after renal transplantation – according to their medical record – probably due to the use of cyclosporine (see illustration 1). Many other studies have reported this phenomenon in ESRD patients after renal transplantation.[34;35] Thomason and colleagues[35] reported gingival overgrowth in 30% of transplanted patients after the use of cyclosporine. As an alternative, tacrolimus can be used which has shown to be successful as an immunosuppressant with less gingival overgrowth.[36]

Although two patients displayed gingival overgrowth, the average bleeding scores did not increase but slightly decreased in the NTx group, after renal transplantation. In a study with 32 transplant patients on immunosuppressive therapy, it was found that pocket depths, plaque and gingivitis scores did not change significantly before and after renal transplantation.[37] In our study, the percentage of teeth, which showed bleeding on probing decreased in both the dialysis and transplanted patients. A study comparing 36 HD patients with 36 controls revealed no statistically significant difference for the periodontal status between these two groups.[11] The decreased levels of bleeding on probing we have found, illustrate less acute inflammation of the gingiva. This might be associated with improved oral hygiene procedures, reduced dental plaque-scores or the immunosuppressive drugs.[11;38] The oral hygiene measures, however, remained the same throughout the study period (data not shown). Also

the level of dental plaque did not differ between baseline and after two years, which is in accordance with Rahman and colleagues[10], who found no differences in sulcular bleeding index score or gingival index score between healthy subjects, patients on HD or those after renal transplantation.

CONCLUSION

Oral health aspects such as caries, dental plaque, gingival bleeding and periodontal indices did not change remarkable after a two-year period in ESRD patients remaining on dialysis and those who received a renal transplant. Regular dental examination and instruction in patients awaiting a renal transplantation is of vital importance to ensure optimal oral health, in order to remain foci free to prevent rejection of the allograft after transplantation. Decreased levels of xerostomia and thirst were observed in patients after renal transplantation, which could add to the quality of life of these patients.

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6

CHEWING GUM AND A SALIVA SUBSTITUTE ALLEVIATE THIRST AND XEROSTOMIA IN PATIENTS ON HEMODIALYSIS

Casper P. Bots, Henk S. Brand, Enno C.I. Veerman, Johanna C. Korevaar, Marianne Valentijn-Benz, Pieter D. Bezemer, Robert M. Valentijn, Pieter F. Vos, Joost A. Bijlsma, Piet M. ter Wee, Barbara M. Van Amerongen, Arie V. Nieuw Amerongen

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ABSTRACT

Background

Most patients on hemodialysis (HD) have to maintain a fluid restricted diet to prevent a high interdialytic weight gain (IWG). The prevalence of xerostomia (the feeling of a dry mouth) is higher in HD patients than in controls. Recently, we demonstrated that xerostomia and thirst were positively related with IWG in HD patients. Thus, this may play a role as a stimulus for fluid intake between dialysis sessions. The aim of the present study was to investigate the effect of chewing gum or a saliva substitute on xerostomia, thirst and interdialytic weight gain (IWG).

Material and methods

This study was a randomised two-treatment crossover design with repeated measures. After the 2-weeks use of chewing gum or saliva substitute, a washout period of two weeks was introduced and hereafter the other regimen was carried out. Xerostomia (XI), thirst (DTI), IWG and the salivary flow rates were assessed at baseline and after each treatment period.

Results

Sixty-five HD patients (42 men: 54.6 ± 14.1 years; 23 women: 54.7 ± 16.3 years) participated in this study. Chewing gum decreased xerostomia (XI) from 29.9 ± 9.5 to 28.1 ± 9.1 ($P < 0.05$). Chewing gum as well as a saliva substitute reduced thirst significantly ($P < 0.05$), but no differences occurred for the average IWG or the salivary flow rates.

Conclusion

The use of chewing gum and, to a lesser extent, a saliva substitute, may alleviate thirst and xerostomia in some HD patients.

INTRODUCTION

Most patients with end stage renal disease (ESRD) on hemodialysis (HD) have to maintain a fluid restricted diet in order to prevent fluid overload between dialysis sessions. High fluid intake through beverages and food, results in high interdialytic weight gain (IWG) between dialysis sessions. Long term non-compliance to the fluid restricted diet can induce complications such as hypertension, acute pulmonary edema, congestive heart failure and cardiovascular comorbidity.[1,2]

Several strategies have been advocated to reduce fluid intake and IWG in HD patients, such as the administration of an angiotensin-converting enzyme (ACE) inhibitor, dietary measures or, ultimately, increasing the frequency of HD sessions.[3] In 25 chronic HD patients with fluid overload, enalapril (an ACE-inhibitor) modestly decreased interdialytic weight gain (IWG) from 0.90 to 0.73 kg per day. Dietary measures, such as the restriction of sodium intake or reducing high protein intake have shown to be effective in reducing IWG in HD patients. However, compliance to the fluid restriction is also influenced by other factors, such as hormonal derangements, social- and psychological changes, thirst (the urge to drink) and xerostomia. Xerostomia is a symptom, defined as the subjective feeling of a dry mouth.[4] Hyposalivation, on the other hand, is the objective measured reduction in salivary flow rate. The prevalence of both hyposalivation and xerostomia is higher in HD patients than in healthy controls.[5,6] Patients with xerostomia report increased water consumption to facilitate eating and speech.

Recently, we demonstrated that xerostomia in HD patients was positively associated with IWG and thirst and, therefore, could play a role as a stimulus for fluid intake between dialysis sessions.[4] Besides an effect on fluid intake, oral dryness also has an impact on the oral health and on the quality of life of the xerostomic patients.

Xerostomia can potentially be improved by mechanical and gustatory stimulation of the salivary glands or by palliative care such as saliva substitutes.[7] In a pilot study with seven non-compliant HD patients, the use of a saliva-substitute reduced the number of dialysis sessions with a high IWG.[8] This suggests that saliva substitutes or stimulants could potentially be used to decrease xerostomia and thus the urge to drink in HD patients. This may increase compliance to the fluid restricted diet and could subsequently result in a decreased IWG and an improved quality of life.

The aim of this clinical crossover trial was to investigate the potential effect of the use of sugar-free chewing gum and a saliva substitute on xerostomia, thirst and IWG in ESRD patients on hemodialysis.

SUBJECTS AND METHODS

Participants and crossover design

One hundred thirty seven ESRD patients undergoing HD were approached in the participating dialysis centers. The inclusion criteria were: at least 3 months on HD, 18 years or older and mentally and physically being able to participate and complete the study. This study was approved by the Medical Ethic Committee of the Vrije Universiteit Medical Center, Amsterdam, The Netherlands.

During the six-week crossover trial, the patients randomly received either chewing gum or the saliva substitute regimen. After a washout period of two weeks, to control for any crossover effect between products, the other regimen (chewing gum or saliva substitute) was tested.

The low-tack, menthol-containing sugar-free chewing gum was Freedent White™ (Wm. Wrigley Jr. Company, Chicago, USA), sweetened with xylitol and sorbitol. To get optimal patient compliance, two flavors of this chewing gum (Sweetmint® and Winterfresh®) were selected in a study with healthy subjects (see Appendix),[9] and a pilotstudy among twenty HD patients (data not shown). The participants were instructed to chew one or two pieces of gum gently, for at least 10 minutes, six times a day and as desired throughout the day when the mouth felt dry or when they were thirsty.

The saliva substitute used in this study was Xialine™ (Lommerse Pharma B.V., Oss, the Netherlands), which contains 0.92% xanthan gum and 2 ppm sodium fluoride. Two bottles (each with 50 mL artificial saliva) were offered to the participants, who were instructed to use the spray at least six times a day and as desired throughout the day when the mouth felt dry or when they were thirsty.

Age, gender, ethnic background, denture wearing, smoking habits and use of alcohol were assessed with a questionnaire. The causes for the ESRD were classified according to the European Renal Association – European Dialysis and Transplantation Association. Clinical data at baseline, such as systolic and diastolic blood pressure (SDP, DBP), normalized Protein Catabolic Rate (*n*PCR) and weekly removal of urea by dialysis (Kt/V_{week}) were retrieved from patient files.

Xerostomia, thirst and Kidney Disease Quality of Life

At baseline, and at the beginning and end of each experimental period, the main parameters: xerostomia (XI), thirst (DTI), IWG and salivary flow rates were determined. The Kidney Disease Quality of Life (KDQOL) was assessed at baseline of the trial to compare to the study population with a reference population.

The Xerostomia Inventory (XI) was used to quantify the perceived xerostomia. The XI is a validated questionnaire with 11 items, each with a five-point Likert-type scale (never = 1 to

very often = 5). The scores are summed, and provide an individual XI score ranging from 11 (no dry mouth) to 55 (extremely dry mouth).[4,10]

Thirst was assessed by using a shortened version of the Dialysis Thirst Inventory (DTI) quantifying the occurrence of thirst before, during and after dialysis and perceived thirst during day and night.[4] Each item has a five-point Likert-type scale (never = 1 to very often = 5). The responses to the five items were summed, which results in a score ranging from 5 (never thirsty) till 25 (very often thirsty).

The Kidney Disease Quality of Life (KDQOL) was measured using the short version of the validated KDQOL-SF™ based on 36 items that focus on health-related concerns of individuals with kidney disease on hemodialysis.[11] These items are assigned to three kidney disease related dimensions and to two generic dimensions; a) symptom problem list; b) effects of kidney disease; c) burden of kidney disease; d) SF-12 physical health; e) SF-12 mental health. The item scores were aggregated without weighting and transformed linearly to a 0-100 range, with higher scores indicating better states.

Interdialytic Weight Gain (IWG)

Patients were weighed before and after each dialysis session. IWG was defined as the amount of fluid (kg) removed during the session (weight predialysis minus weight postdialysis) with the assumption that all the weight gained in the previous interdialytic interval had been lost during the dialysis session. The IWG was calculated and expressed as the mean IWG during a period of two weeks.[4]

Saliva collection

Unstimulated whole saliva (UWS) and paraffin chewing stimulated whole saliva (CH-SWS) were both collected before dialysis. All subjects were instructed to refrain from smoking, eating, drinking and tooth brushing for one hour prior to saliva collection. UWS was collected according to the spitting method, with some small modifications.[4] Before collection, the subjects rinsed their mouth with tap water. The collection started with the instruction to void the mouth of saliva by swallowing. Saliva was allowed to accumulate on the floor of the mouth and the subjects were instructed to spit into pre-weighed test tubes every 30 seconds. The saliva collection period was five minutes.

Paraffin chewing stimulated whole saliva (CH-SWS) was collected for five minutes using a tasteless piece of parafilm (5 x 5 cm; 0.30 g; Parafilm "M", American National CAL, Chicago, USA). The chewing stimulated saliva was also spitted out into pre-weighed test tubes every 30 seconds for five minutes. During the saliva collection period, the subjects chewed at their natural pace. Saliva volumes were determined gravimetrically (assuming 1 g = 1 mL).

Statistical methods

The data at baseline were stratified with regard to gender, age (≤ 64 year; > 64 year), residual urine output (yes/no) and full-denture (yes/no) and analyzed with an ANOVA. The period effect and the influence of the order in which the subjects received the therapy (treatment-period interaction) were investigated with two sample *t*-tests. Since no treatment-period interaction was found, we compared the effect of each therapy (chewing gum and saliva substitute) to the main baseline variables using the General Linear Model of ANOVA – repeated measures design, followed by paired *t*-tests as post-hoc procedure. To explore the effect of gender, age, residual urine output and full-denture, these variables were separately imputed in the model as between-subject factors. The data of the five dimensions of the KDQOL-SF™ were compared with the reference population using paired *t*-tests. The statistical analysis was performed using the statistical software package SPSS (version 10.0, SPSS Inc., Chicago, IL, USA). All data are presented as mean ± SD, and levels of significance were set at $P < 0.05$.

RESULTS

Patients demographics

One hundred thirty seven HD patients were approached to participate in this study. After explanation of the aim and design of the study, eighty-nine patients gave informed consent for participation and entered the study. Main reasons for not participating in the study were no thirst (n = 36), not interested (n = 6) or illness (n = 5). Of the eighty-nine HD patients who entered the study, 65 (73%) of the initial sample completed the six-week crossover clinical trial: 42 men and 23 women (mean age 54.6 ± 14.1 and 54.7 ± 16.3 years, respectively). Reasons for withdrawal during the trial were holidays (n = 4), language problems (n = 3), no xerostomia or thirst (n = 2), transplanted during study (n = 2), illness of the patient (n = 1) or other reasons not related to the intervention (n = 12). Causes for the chronic renal failure were renal vascular disease due to hypertension (15.4%), polycystic kidneys (12.3%), diabetes type 2 (6.2%), miscellaneous (26.1%) or unknown (40%). The clinical and socio-demographical data at baseline are presented in Table 1.

Baseline: XI, DTI, IWG and KDQOL

At baseline, differences were observed for the XI score, the DTI score and IWG for patients younger than 65 and those without residual urine output (see Table 2). The level of xerostomia, thirst and IWG were significantly higher in the younger age group compared to individuals over 65 years. Patients with residual urine output had less xerostomia and thirst, and a significant lower IWG than those without residual urine output. The baseline values of the KDQOL-SF in our study population were comparable to a reference population of 428 HD patients in The Netherlands[12], thus representing a normal Dutch HD population (see Table 3).

Table 1. Demographic and clinical data at baseline (n = 65)

Age (years) (SD)		54.6 (14.8)	
Male gender		64.6%	(n = 42)
Diabetes type 1 or 2		15.4%	(n = 10)
Residual Urine Output		27.7%	(n = 18)
Full denture		32.3%	(n = 21)
Current smoker		26.2%	(n = 17)
Alcohol use		38.5%	(n = 25)
Educational level	*Primary school*	21.5%	(n = 14)
	Secondary school	35.4%	(n = 23)
	High school or higher	43.1%	(n = 28)
Ethnical background	*Dutch*	60.0%	(n = 39)
	Indonesian	7.7%	(n = 5)
	Surinam	6.2%	(n = 4)
	Maroc	7.7%	(n = 5)
	Other	18.5%	(n = 12)
Time on HD (months)		27.1 (24.0)	(n = 4)
HD sessions per week	2	6.1%	(n = 4)
	3	90.8%	(n = 59)
	> 3	3.1%	(n = 2)
IWG (kg)		2.1 (0.9)	
IWG/day (kg/day)		0.94 (0.47)	
SBP *before* (mm Hg)		146.1 (18.9)	
DBP *before* (mm Hg)		80.5 (9.2)	
SBP *after* (mm Hg)		131.3 (19.0)	
DBP *after* (mm Hg)		74.4 (11.0)	
Kt/V urea *week*		4.2 (0.9)	
nPCR (g/kg/day)		1.17 (0.31)	
Albumin (g/L)		36.0 (4.4)	

Mean values (SD) are given for continuous variables. IWG, SBP and DBP are mean values of the dialysis sessions that took place during the 2 weeks before the baseline measurements. **Abbreviations:** IWG, interdialytic weight gain; Kt/V *week,* average removal of urea expressed per week; *n*PCR, normalized protein catabolic rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Crossover study: effect on XI, DTI and IWG

A significant treatment effect was observed for xerostomia ($P = 0.024$) and thirst ($P = 0.015$), see Table 4a. The use of chewing gum decreased the level of perceived xerostomia significantly from XI = 29.9 ± 9.5 at baseline to XI = 28.1 ± 9.1 after gum chewing ($P = 0.005$). Both chewing gum and the saliva substitute had a positive overall effect on the perceived thirst (DTI score) during the crossover clinical trial. Stratification of preference for the chewing gum (Sweetmint®; Winterfresh®) showed no different treatment effect. The IWG during treatment with chewing gum or the saliva substitute did not differ from the average IWG measured at baseline, see Table 4a. Also the systolic and diastolic blood pressure showed no effect of saliva substitute or chewing gum (data not shown).

Table 2. Xerostomia (XI), thirst (DTI), Interdialytic weight gain (IWG), unstimulated whole saliva (UWS) and parafilm chewing stimulated whole saliva (CH-SWS) *at baseline* (n = 65)

		XI (11-55)	DTI (5-25)	IWG (kg)	UWS (mL/min)	CH-SWS (mL/min)	n
Gender	*Male*	28.7 (8.5)	16.8 (5.1)	2.2 (1.0)	0.32 (0.28)	0.95 (0.53)	42
	Female	32.0 (10.9)	16.4 (5.3)	1.9 (0.8)	0.26 (0.16)	0.90 (0.74)	23
Age group	*≤ 64 years*	31.7 (9.3)*	17.7 (4.4)*	2.3 (0.9)*	0.32 (0.27)	0.96 (0.62)	46
	> 64 years	25.5 (8.7)	14.0 (5.9)	1.6 (0.7)	0.24 (0.16)	0.88 (0.61)	19
Residual Urine Output	*Yes*	24.7 (7.9)	13.9 (5.4)	1.4 (0.8)	0.32 (0.18)	0.96 (0.48)	18
	No	31.9 (9.4)*	17.7 (4.7)*	2.4 (0.8)**	0.28 (0.27)	0.93 (0.66)	47
Full denture	*Yes*	30.5 (11.3)	15.5 (6.6)	1.8 (1.0)	0.33 (0.37)	1.00 (0.59)	21
	No	29.8 (8.5)	17.4 (4.1)	2.2 (0.8)	0.28 (0.17)	0.90 (0.63)	44

Data were analyzed with an ANOVA, * $P < 0.05$; * * $P < 0.01$.

Table 3. Overview of the five dimensions of the Kidney Disease Quality of Life (KDQOL) at baseline compared to a reference population[12]

KDQOL dimensions	Study (n = 65)	NECOSAD (n = 428)
Symptom Problem	77.6 (13.7)	74.8 (15.6)
Effect Kidney Disease	73.0 (17.2)	69.3 (19.4)
Burden Kidney Disease	48.8 (24.0)	45.9 (25.5)
SF-12 Physical	37.1 (11.4)	36.1 (9.8)
SF-12 Mental	47.0 (9.6)	45.8 (10.3)

Data are analyzed with Students *t*- tests. No significant differences were observed.
NECOSAD = Netherlands Cooperative Study on Adequacy of Dialysis.

Gender, age and wearing a full denture had no effect on the response to the different treatment modalities. However, a significant interaction was observed for residual urine output with the XI scores. In patients without residual urine output the XI scores decreased significantly from 31.9 ± 9.4 at baseline to 29.3 ± 9.1 after gum chewing ($P = 0.003$) and to 30.6 ± 9.5, after saliva substitute ($P = 0.038$), see Table 4b.

In HD patients with thirst, an overall treatment effect of chewing gum and saliva substitute on thirst (DTI) and xerostomia (XI) was found (Table 4b). Chewing gum reduced both the XI and the DTI score. In patients with thirst, the saliva substitute had no effect on the level of xerostomia. Patients with thirst had significantly higher IWG values than those without thirst. However, neither gum nor spray did affect the IWG in the 'thirst group'. No significant difference was found for the number of patients with diuresis between the 'thirst' group and the 'no thirst' group.

In patients with hyposalivation (UWS ≤ 0.15 mL/min), an overall treatment effect was found on the XI scores. Gum chewing reduced the XI scores significantly from 33.2 ± 9.1 to 29.7 ± 8.4 ($P < 0.05$, see Table 4b). During both treatment modalities, the DTI levels were comparable between both groups (see Table 4b) and no overall treatment effect was found. Patients with hyposalivation and those with normal salivary flow rates did not differ with respect to the IWG. Also, the treatment did not have an effect on the IWG.

Table 4a. The effect of the two treatment modalities (chewing gum and saliva substitute for two weeks) on the main outcome variables in 65 HD patients

	XI (11-55)	DTI (5-25)	IWG (kg)	UWS (mL/min)	CH-SWS (mL/min)
Baseline	29.9 (9.5)	16.6 (5.1)	2.09 (0.9)	0.26 (0.2)	0.89 (0.5)
Chewing gum	28.1 (9.1)*	15.4 (4.8)*	2.07 (0.9)	0.28 (0.2)	0.81 (0.4)
Saliva substitute	29.0 (9.6)	15.5 (5.0)*	2.08 (1.0)	0.30 (0.2)	0.89 (0.5)
Treatment (p)	*0.024*	*0.015*	*n.s*	*n.s.*	*n.s.*

In the vertical rows, the main outcome variables: xerostomia (XI_{11-55}), thirst (DTI_{5-25}), Interdialytic weight gain (IWG_{kg}), unstimulated whole saliva ($UWS_{mL/min}$) and chewing stimulated whole saliva ($CH\text{-}SWS_{mL/min}$) are presented. *In italics* the *P*-values of the effect of sequence and overall treatment (repeated measures MANOVA). The two treatment modalities (chewing gum and saliva substitute) are compared to baseline and tested with a GLM-ANOVA, followed by paired *t*-tests as post-hoc procedures; * $P < 0.050$.

Table 4b. The effect of the two treatment modalities (chewing gum; saliva substitute) on the xerostomia (XI), thirst (DTI) and interdialytic weight gain (IWG) with regard to residual urine output, hyposalivation and thirst

	Residual Urine Output; n = 18			No Residual Urine Output; n = 47		
	XI (11-55)	**DTI (5-25)**	**IWG (kg)**	**XI (11-55)**	**DTI (5-25)**	**IWG (kg)**
Baseline	24.7 (7.9)	13.9 (5.4)	1.4 (0.8)	31.9 (9.4)#	17.6 (4.7)#	2.4 (0.8)#
Chewing gum	24.7 (8.7)	12.8 (4.9)	1.3 (0.8)	29.3 (9.1)**	16.4 (4.3)#	2.4 (0.7)#
Saliva substitute	24.8 (8.6)	12.2 (5.5)	1.3 (0.8)	30.6 (9.5)*/#	16.7 (4.3)#	2.4 (0.9)#
Treatment (P)	*n.s*	*n.s.*	*n.s.*	*P* < 0.05	*n.s.*	*n.s.*
	No thirst (DTI 5-15); n = 26			**Thirst (DTI 16-25); n = 39**		
	XI (11-55)	**DTI (5-25)**	**IWG (kg)**	**XI (11-55)**	**DTI (5-25)**	**IWG (kg)**
Baseline	22.8 (6.0)	11.4 (3.5)	1.8 (0.9)	34.5 (8.6)$	20.1 (2.3)$	2.3 (0.9)$
Chewing gum	22.5 (7.3)	12.2 (4.5)	1.7 (0.9)	31.6 (8.6)**/$	17.6 (3.6)**/$	2.3 (0.8)$
Saliva substitute	21.2 (5.5)	11.7 (3.9)	1.8 (1.2)	33.8 (8.6)$	18.0 (4.1)**/$	2.2 (0.8)
Treatment (P)	*n.s*	*n.s*	*n.s.*	*P* < 0.05	*P* < 0.001	*n.s.*
	No hyposalivation (> 0.16 mL/min); n = 46			**Hyposalivation (< 0.15 mL/min); n = 19**		
	XI (11-55)	**DTI (5-25)**	**IWG (kg)**	**XI (11-55)**	**DTI (5-25)**	**IWG (kg)**
Baseline	28.5 (9.4)	15.9 (5.5)	2.1 (1.0)	33.2 (9.1)Ø	18.4 (3.7)	2.1 (0.7)
Chewing gum	27.4 (9.5)	14.8 (4.7)	2.1 (1.0)	29.7 (8.4)**	17.2 (4.6)	2.0 (0.7)
Saliva substitute	27.3 (9.4)	14.8 (5.3)	2.1 (1.0)	33.0 (9.1)Ø	17.2 (3.9)	2.1 (1.0)
Treatment (P)	*n.s*	*n.s.*	*n.s.*	*P* < 0.05	*n.s.*	*n.s.*

In the vertical rows, the main outcome variables: xerostomia (XI_{11-55}), thirst (DTI_{5-25}) and interdialytic weight gain (IWG_{kg}). *In italics* the *P*-values of the effect of the overall treatment (repeated measures MANOVA). The two treatment modalities (chewing gum and saliva substitute) are compared to baseline and tested with a GLM-ANOVA, followed by paired *t*-tests as post-hoc procedure; *n.s. = no statistical significance; * $P < 0.05$; ** $P < 0.001$*. Values indicated with (#,$,Ø) in the right column ('No residual urine output', 'thirst', 'hyposalivation') differ statistically significant with the corresponding value in the left column (One-Way ANOVA).

In a subgroup of HD patients (n = 12) without residual urine output, suffering from thirst (DTI = 16-25) and hyposalivation (UWS ≤ 0.15 mL/min) the highest mean XI values were observed. A significant reduction of the XI score was observed after the use of chewing gum for two weeks from 37.8 ± 7.2 to 32.6 ± 6.6. The use of a saliva substitute, however, did not affect the XI score. In this subgroup, no treatment effects were found for the level of thirst (DTI) and IWG (data not shown).

Saliva secretion: at baseline and effect therapy

UWS and CH-SWS flow rates showed a skewed distribution and were square root transformed before statistical analyses. For clarity, the untransformed data are presented. At baseline, the mean UWS was 0.26 ± 0.15 mL/min (median = 0.24; range = 0.01-1.80). The CH-SWS was 0.89 ± 0.44 mL/min (median = 0.82; range = 0.18-3.78). Treatment with chewing gum or the saliva substitute did not influence the UWS and CH-SWS (Table 4a).

DISCUSSION

Thirst and xerostomia are major problems for patients on hemodialysis.[4,6,13,14] Oral-pharyngeal factors, such as a dry mouth, have been associated with thirst.[4] Therefore it is feasible that mechanical stimulation of saliva secretion by chewing gum potentially could reduce thirst.

This study is the first large-scale clinical crossover study to investigate the effect of chewing gum and a saliva substitute on xerostomia (XI), thirst (DTI) and IWG in patients on hemodialysis. Overall, the use of chewing gum during two weeks among HD patients significantly reduced both thirst and xerostomia. This is in agreement with other studies that investigated the effect of chewing gum on xerostomia in other patient populations, such as rheumatic patients[15] or in patients with a malignant disease.[16] Besides the role of oral dryness, also other factors such as sodium intake, high plasma sodium, potassium depletion, angiotensin II levels, rapid increases in plasma urea and psychological factors play role in the multi-complexity of thirst and fluid intake among HD patients.[4,13,17,18]

In this study the use of a saliva substitute by HD patients reduced perceived thirst but had no effect on xerostomia. In the literature, conflicting data about the efficacy of saliva substitutes have been presented. In thirty patients with radiation-induced xerostomia, feelings of a dry mouth decreased after the use of a saliva substitute. However, other studies failed to show a substantial effect of saliva substitutes after radiation therapy or in patients with Sjögren's syndrome.[7,19]

Although the effect of the therapy on the XI and DTI score was modest, the majority of patients (72.3%) rated chewing gum as a beneficial therapy. Chewing gum was also rated best with respect to effectiveness, easiness to use and taste compared to the saliva substitute (see Chapter 7). Therefore, chewing gum seems preferable in the reduction of oral dryness and thirst among HD patients.

The mean salivary flow rates were normal and comparable, both to reference values for healthy individuals and to other studies in HD patients.[14] In general, patients with severe hyposalivation respond best on saliva substitutes.[7] This is in contrast to our study, in which gum chewing reduced xerostomia best in the subgroup with hyposalivation (UWS ≤ 0.15 mL/min). The most plausible reason is that the xerostomia and hyposalivation in other investigations is of different origin.[7,19,20] Since it is likely that salivary glands are not affected by the

HD treatment,[4] mechanically or gustatory activation by chewing is still possible, in contrast to patients suffering from severe Sjögren's syndrome.

Previously, we have shown that thirst is significantly related to IWG.[4] Compliance to the fluid restricted diet (500 mL/day) was measured by IWG. Although gum chewing and spraying with a saliva substitute significantly reduced thirst, the IWG in HD patients was not affected. Several patients indicated that chewing and spraying had a distracting effect and resulted in postponing fluid intake, however, the net fluid intake remains the same in the study period. This might be explained because the patients know how much weight they are allowed to gain between dialysis and thus drink, although no thirst is present. It might also be possible that a two-week period is too short to affect the fluid intake and thus the IWG. The contribution of fluid intake due to the use of artificial saliva was negligible, since the average volume of artificial saliva used did not exceed 7 mL/day.

A potential limitation of this study is the lack of blinding. However, this is unavoidable in this crossover design in which the participant received two potential active agents (chewing gum and saliva substitute).

CONCLUSION

This crossover clinical trial shows that a saliva stimulating agent (chewing gum) and a saliva substitute both induced a modest reduction in the level of thirst (DTI) in HD patients. The level of xerostomia (XI) was reduced after the use of chewing gum. However, no evidence of reduced fluid intake or weight gain could be obtained. HD patients younger than 65 years without residual urine output have to deal most with thirst and xerostomia and could therefore benefit from chewing gum or artificial saliva. Therefore, we conclude that the use of chewing gum, and to a lesser extent a saliva substitute, may alleviate thirst and xerostomia in some HD patients on a fluid restricted diet and thus should be considered as a clinical tool to assist HD patients in maintaining to the fluid restricted diet.

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7

THE MANAGEMENT OF XEROSTOMIA IN PATIENTS ON HEMODIALYSIS: COMPARISON OF ARTIFICIAL SALIVA AND CHEWING GUM

Casper P. Bots, Henk S. Brand, Enno C.I. Veerman, Marianne Valentijn-Benz, Barbara M. Van Amerongen, Robert M. Valentijn, Pieter F. Vos, Joost A. Bijlsma, Pieter D. Bezemer, Piet M. ter Wee, Arie V. Nieuw Amerongen

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ABSTRACT

Introduction

Many patients on hemodialysis therapy (HD) suffer from a dry mouth and xerostomia. This can be relieved by mechanical and gustatory stimulation or palliative care. The aim of this crossover study was to investigate the effect and preferences of a sugar-free chewing gum (Freedent White™) and a xanthan gum-based artificial saliva (Xialine™) in the management of xerostomia in chronic HD patients.

Material and Methods

Sixty-five HD patients participated in a six-week crossover trial. The artificial saliva was rated significantly lower than the chewing gum for effectiveness, taste and global assessment.

Results

No preference differences were found for gender and age, although older subjects rated the artificial saliva with a higher mark. Thirty-nine subjects (60%) preferred chewing gum, 15% (n = 10) preferred the artificial saliva.

Conclusion

Both chewing gum and artificial saliva could play an important role in the palliative care of xerostomia in HD patients.

INTRODUCTION

The major function of the kidneys is the removal of metabolic waste products, electrolytes and water. If this function is impaired to a fatal level, end stage renal disease (ESRD) occurs leading to death, unless renal replacement therapy is started. Chronic dialysis therapy such as hemodialysis (HD) has proven to be successful in prolonging the life of these patients. During HD treatment, an artificial kidney is used for several hours, three or four times a week, to clarify blood of waste products and excess fluid. Patients on HD therapy have several oral complications among others an impaired salivary flow rate and an increased subjective sensation of a dry mouth (xerostomia).[1] The prevalence of xerostomia in HD patients ranges between 33 and 76%.[2-4] The patients' quality of life (QoL) and oral health are negatively influenced by a dry mouth.[5,6] Besides a direct effect of the HD treatment on the level of xerostomia, also other factors such as medication, depression or forthcoming stress from the HD treatment may contribute to the perceived xerostomia.[7-11]

A slight or moderate level of xerostomia can be alleviated by mechanical and gustatory stimulation of the salivary glands using chewing gum or lozenges. Severe xerostomia can be ameliorated by parasympathetic stimulation (pilocarpine) or palliative care such as artificial saliva.[12,13] Most studies in this research field focused on either the effect of an artificial saliva or a saliva stimulant in patients after radiation therapy in the oral-facial region or in those with Sjögren's syndrome.[12,14-17] This is the first study to compare the use of both artificial saliva and chewing gum in chronic HD patients.

We aimed to investigate which therapy – sugar-free chewing gum or artificial saliva – was preferred most in the management of xerostomia in ESRD patients on hemodialysis.

METHODS

Participants and design of the study

This multi-center study was conducted at the Vrije Universiteit Medical Center (Amsterdam), The Rode Kruis Hospital (The Hague) and Stichting DIANET Dialysis Centers (Amsterdam and Utrecht). The study protocol was approved by the Medical Ethical Committee of the Vrije Universiteit Medical Center, Amsterdam, The Netherlands.

At the different dialysis centers, one hundred thirty seven ESRD patients, undergoing were approached. The inclusion criteria were more than three months on HD, > 18 years of age and mentally and physically being able to participate and complete the study. After explanation of the aim and design of the study, eighty-nine patients gave informed consent for participation and entered the study. Sixty-five (73%) of the patients completed the six-week crossover clinical trial (see Figure 1).

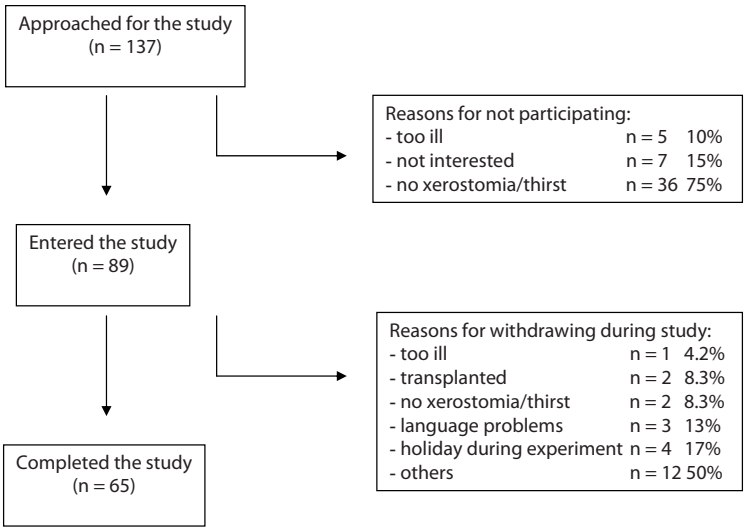

Figure 1. Profile of the study

The study was a six-week crossover trial. At the beginning and end of each two-week test period, the level of perceived xerostomia was measured and the effectiveness of the treatment was assessed. After baseline measurements, patients were randomly allocated to either chewing gum or the artificial saliva regimen. A two-week washout period was introduced to control for potential crossover effects between products. Subsequently, the other regimen (chewing gum or artificial saliva) was tested (Figure 2).

The chewing gum used in this study was Freedent White™ (Wm. Wrigley Jr. Company, Chicago, USA), a low-tack, and menthol-containing but sugar-free chewing gum. To get optimal patient compliance, two flavors of the same type of chewing gum (Sweetmint:

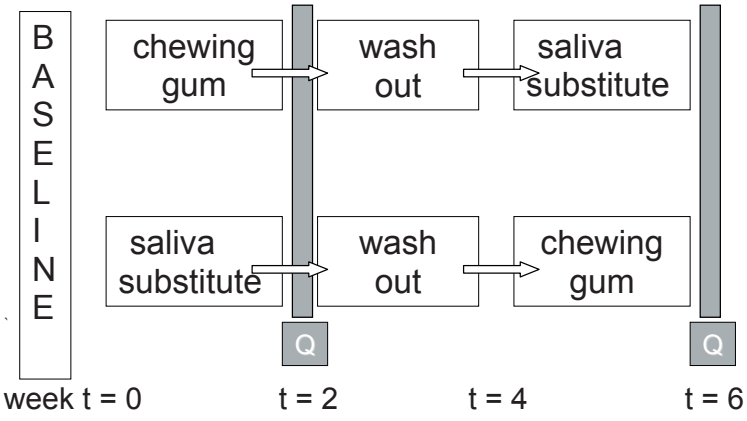

Figure 2. Crossover study design: each test period was two weeks. After each test period a questionnaire (Q) was distributed to assess the level of xerostomia (XI), the preferences and the effect of the treatment.

Table 1. Responses to the different items of the questionnaire, concerning the effect of the two therapies (n = 65)

		Artificial saliva	Chewing gum	
Easiness to use the product	VAS not easy – very easy	6.7 (2.9)	7.6 (2.3)	$P < 0.050$
Effect on relieving **thirst**	VAS not effective – very effective	3.3 (2.6)	5.5 (2.7)	$P < 0.001$
Effect on relieving **dry mouth**	VAS not effective – very effective	4.3 (2.8)	6.5 (2.5)	$P < 0.001$
Judgment of **taste**	VAS unpleasant – pleasant	6.0 (2.5)	7.3 (2.2)	$P < 0.050$
	VAS nasty – delicious	5.5 (2.0)	7.3 (2.0)	$P < 0.001$
	VAS mild – strong	2.7 (1.9)	4.5 (2.7)	$P < 0.001$
Global assessment (mark 1-10)		5.6 (2.1)	7.1 (1.6)	$P < 0.001$
The therapy was beneficial		43% (n = 28)	72% (n = 47)	$P < 0.001$
Willingness to use the therapy during a longer time		39% (n = 25)	70% (n = 46)	$P < 0.001$

Data are presented as mean (SD) and were analyzed using non-parametric Wilcoxon tests. Chi-square tests were applied on the reply to the questions "Was the therapy beneficial" and "Are you willing to use the therapy during a longer time".

mild; Winterfresh : strong) were selected and given to the patients.[18] The participants were instructed to chew one or two pieces of gum gently, six times a day for at least 10 minutes and as desired throughout the day when their mouth felt dry. The artificial saliva used was Xialine™ (Lommerse Pharma B.V., Oss, Holland), based on xanthan gum. The participants were instructed to use a dose of three sprays at least six times a day, and as desired throughout the day and night when the mouth felt dry.

At baseline and at the end of each therapy, the level of xerostomia was assessed with the Xerostomia Inventory (XI). This is a validated questionnaire with 11 items. Each item has a five-point Likert type scale (never = 1 to very often = 5) and the scores are summed which provides an individual XI score ranging from 11 (no dry mouth) to 55 (extremely dry mouth).[19] At the end of each treatment period, a questionnaire (100mm visual analogue scale = VAS) was used to assess the effectiveness, preferences and side effects of the treatment, see Table 1.[18]

Statistical methods

The data of the 65 patients who completed the crossover study were analyzed and are presented. First, we assessed the potential effect of sequence (chewing gum-artificial saliva vs artificial saliva-chewing gum) on the level of xerostomia (XI). Since sequence did not affect the XI-level, we investigated the overall treatment effect of each therapy with repeated-measures multivariate analysis of variance (MANOVA). Hereafter, we investigated the effect of each therapy compared to BASELINE for the level of xerostomia using a General Linear Model of ANOVA – repeated measures design, followed by paired *t*-tests as *posthoc* procedure when appropriate. The differences between the data of the VAS-scales were analyzed using non-parametric tests and the other data from the questionnaire were analyzed using chi-square tests. Separately, the differences between gender, age (≤ 64 years vs > 64 years) and xerostomia (XI score ≤ 33 or > 33) were analyzed. The statistical analysis was performed

using the statistical software package SPSS (version 10.0, SPSS Inc., Chicago, IL, USA). All data are presented as mean ± SD and levels of significance were set at $P < 0.05$.

RESULTS

One hundred thirty seven HD patients were approached to participate in the study. Eighty-nine patients gave informed consent and entered the study (see Figure 1). Reasons for not participating in the study were illness (n = 5), no xerostomia or thirst (n = 36) and not interested (n = 7). Sixty-five (73%) patients entered the study and completed the six-week crossover clinical trial: 42 men and 23 women (mean age 54.6 ± 14.1 and 54.7 ± 16.3 years, respectively), which represent the general Dutch population receiving hemodialysis treatment. At baseline, the mean time of treatment with HD was 27.1 ± 24.0 months.

Overall, artificial saliva was rated significantly lower than the chewing gum on each item of the questionnaire (see Table 1). In the artificial saliva group, the mean VAS score for the effect of the therapy relieving a dry mouth (VAS not effective-very effective) was 4.3 ± 2.8 compared to 6.5 ± 2.5, for the chewing gum. The taste of the gum was appreciated significantly more pleasant and delicious (VAS unpleasant-pleasant = 7.3 ± 2.2) than the artificial saliva (VAS unpleasant-pleasant = 6.0 ± 2.5), see Table 1. The global assessment for chewing gum and artificial saliva were respectively, 7.1 ± 1.6 and 5.6 ± 2.1. Nevertheless, a subpopulation of the patients (15%) preferred the use of artificial saliva. No differences were found between the participants and those who initiated but not completed the therapy (data not shown).

The global assessment given by the older patient category (> 64 years) for the artificial saliva was significantly higher than the global assessment given by younger patients (mean 6.6 ± 1.6 and 5.2 ± 2.2, respectively). However, after stratification with regard to gender, age and the level of xerostomia (XI) no significant differences were found for the other items in the questionnaire, neither for the preferences of chewing gum nor artificial saliva.

Table 2. Differences in preferences between artificial saliva and chewing gum

		Artificial saliva	Chewing gum	
Which therapy do you prefer?		15.4% (n = 10)	60.0% (n = 39)	$P < 0.001$
No preference:	6.2% (n = 4)			
None of both:	7.7% (n = 5)			
Not reported:	11% (n = 7)			
Reason for preference:	Effect	60% (n = 6)	92% (n = 36)	$P < 0.005$
	Taste	40% (n = 4)	72% (n = 28)	n.s.
	Easiness to use	80% (n = 8)	74% (n = 29)	n.s.
	Not much side effect	50% (n = 5)	41% (n = 16)	n.s.

Chi-square tests were applied to analyse the differences between artificial saliva and chewing gum.

Table 3. Side effects of artificial saliva and chewing gum (n = 65)

	Artificial saliva		Chewing gum		
Unpleasant taste	28%	(n = 18)	9.2%	(n = 6)	n.s.
Nausea	9.2%	(n = 6)	4.6%	(n = 3)	n.s.
Irritation of the oral mucosa	3.1%	(n = 2)	4.6%	(n = 3)	n.s.
Diarrhea	6.2%	(n = 4)	9.2%	(n = 6)	n.s.
Sensitivity of the jaw	- -		11%	(n = 7)	- -
Fatigue of the muscles	- -		25%	(n = 16)	- -
Sensitivity of the teeth	- -		6.2 %	(n = 4)	- -

Differences between artificial saliva and chewing gum were analyzed using Chi-square tests.

A significant difference was found for the number of HD patients who rated the use of chewing gum beneficial (n = 48; 72%) and those who replied that the use of spray was beneficial (n = 28; 43%). Twenty-five patients (39%) rated chewing gum as the most beneficial therapy in contrast to six patients (9.2%) who chose artificial saliva as most beneficial. Twenty-two patients (34%) judged both therapies as equally beneficial, compared to 8 patients (12%) who reported that both therapies were not beneficial. Seventy one percent (n = 46) of all the patients were willing to use the chewing gum during a longer time, while 39% (n = 25) were willing to use the saliva substitute during a longer time.

The preference for the two different tastes of chewing gum were assessed and revealed no significant differences, although sweetmint was slightly more preferred (n = 24; 37%) than peppermint (n = 18; 28%). Twenty-three patients (35%) had no preference for a specific taste.

At the end of the experiment, the overall preferences were assessed. Thirty-nine (60%) patients preferred chewing gum, while 10 (15%) preferred the artificial saliva. Four patients had no preference; five preferred none of both and seven did not report their preference. The two main reasons for preference of a specific therapy were the overall effect and easiness to use, see Table 2. No difference in preference was found for gender and for age.

Specific side effects related to the therapy were also assessed with a questionnaire (Table 3). Eighteen patients (28%) reported a bad taste as side effect of the artificial saliva compared to six patients (9.2%) after the use of chewing gum. No significant differences were found for the other side effects mentioned. Sixteen patients (25%) using chewing gum reported fatigue in the jaw muscles after chewing during two weeks. An overview of spontaneously given comments, both positive and negative, is presented in Table 4.

Both treatment arms (chewing gum and artificial saliva) demonstrated similar compliance during daytime. Ninety five percent (n = 62) used the chewing gum in the afternoon, compared to 83% (n = 54) in the artificial saliva group. In the night, 26% (n = 17) of the patients used the artificial saliva compared to 9% (n = 6) in the chewing gum group. Chewing gum is used more frequently before (42% ; n = 27) and after (48% ; n = 31) the dialysis session then

Table 4. Overview of comments on the therapies, given spontaneously

CHEWING GUM	
Positive	**Negative**
Positive about chewing (n = 2)	Pain underneath denture during chewing
Pleasant (n = 3)	Pain of muscles in the jaw (n = 2)
Stimulates saliva	Naussea (n = 2)
Less oral dryness (n = 4)	Dryness and hungry after use
Less thirst (n = 2)	Sore gingiva and throat
Pleasant distraction	Taste quickly gone (n = 2)
Does not stick to the teeth	Sweetmint too sweet
Easier than spray	Peppermint too strong
Good alternative for drinking	Unpleasant taste
	Chewing gum sticks to teeth (n = 3)
	Chewing gum too tough
	I don't like chewing
ARTIFICIAL SALIVA	
Positive	**Negative**
Oral cavity feels humid	Taste not fresh (n = 3)
I don't drink water in the night anymore	Not effective (n = 2)
Spray works when I am very dry, e.g. after speeching	Works shortly (n = 4)
Fresh, pleasant spray (n = 2)	Taste of spray can be stronger (n = 2)
Gives a good feeling	I prefer water
	Candy or gum gives more distraction
	Nausea (n = 2)
	Difficult to press on bottle (n = 3)
	Bottles are too big for pocket
	The amount of spray is not consistent
	Thirsty after use (n = 2)
	My throat stays dry (n = 2)
	Mouth dryer than before (n = 2)

during (15% ; n = 10). Artificial saliva showed the same pattern, (23% (n = 15); 17% (n = 11); 7.7% (n = 5), respectively).

DISCUSSION

Patients on hemodialysis (HD) have to maintain a fluid restricted diet to prevent fluid overload. Besides that they suffer from thirst and xerostomia, which has a substantial impact on the quality of life of severely ill patients and those on chronic renal replacement therapy.[6] Oral effects of long-standing xerostomia are an increased frequency of caries, mucosal soreness and an increased risk of oral inflammation.[17] In the management of xerostomia, slight xerostomia can be treated by mechanical or gustatory stimulation (chewing gum), while more severe xerostomia can be treated with parasympathetic stimulation (pilocarpine or

cevimeline) or artificial saliva.[12,13,18,20] This is the first crossover study among HD patients in which the preferences between artificial saliva and chewing gum were compared. It was revealed that, compared with artificial saliva, chewing gum was preferred by the major part of the patients in the palliative treatment of a dry mouth.

The efficacy of chewing gum or saliva substitutes as therapy for xerostomia has previously been investigated in other patient categories. Only a few clinical trials have been carried out in which artificial saliva was tested against the use of chewing gum in a crossover design.[14,21,22] At the end of the trial, 60.0% of the patients (n = 39) preferred the use of chewing gum, compared to 15.2% preferring artificial saliva. These results are in accordance with Davies and co-workers, who conducted a prospective, randomized, open crossover study among forty-one patients with malignancy that experienced from xerostomia.[22] In another study, one hundred and six subjects with low salivary flow rates and long term xerostomia participated. Both the saliva substitutes and stimulants relieved the xerostomic feelings to some extent, but showed no substantial differences. However, the saliva stimulants V6® chewing gum and Salivin® lozenge were ranked as the two best products.[14] This is in accordance with another crossover study in which patient preferences and product efficacy were assessed in eighty subjects with xerostomia and hyposalivation. Although no differences were revealed in the efficacy of the various therapies (chewing gum, lemon lozenges, artificial saliva), the majority of patients preferred the use of a saliva stimulant (70%; n = 56).[21]

In our study we used Xialine™, a saliva substitute based on the natural biopolymer xanthan gum.[23] Xialine™ improved problems with speech and taste perception in patients treated with radiotherapy for head and neck cancer.[24] In a crossover study with forty-three Sjögren's syndrome patients, three saliva substitutes (polymer, gum and mucin-based) were equally effective in the reduction of xerostomia, compared to placebo.[23]

The fact that the participants preferred the chewing gum (Table 1 and 2) could have several reasons. The effectiveness of gum on relieving thirst and a dry mouth was higher, which might be an effect of the saliva stimulating capacity of the gum.[18] Artificial saliva probably works shorter. Using chewing gum might attract less attention in public than spraying and can be carried out easily. In addition, some patients experienced difficulties with pressing the bottle. More advanced bottle designs might enhance the easiness to use the spray. Both therapies contained menthol flavour, intensity differences of this flavour could have influenced the preferences.

Age has no effect on the preferences, but it has a substantial effect on the global assessment. Older HD subjects rated the artificial saliva higher than the chewing gum. This is in accordance with other studies in which older patients preferred use of artificial saliva.[26,27] Several factors may contribute to this observation. It is generally agreed, that the lack of social acceptance of gum chewing in public plays a role in the aged generation. The prevalence of wearing a (partial) denture increases with age, while the amount and density of the jaw muscles decrease during aging.[28] These factors might have hindered during gum chewing.

Since most gum types stick to the denture base, the gum used in this study was a low-tack gum which does not stick to a denture and is therefore better accepted in patients with dentures or metal appliances.[28,29]

In general, chewing gum and artificial saliva are not associated with many side-effects, although intense gum chewing can contribute to temporomandibular joint pain.[30] In our study, respectively 10.8% (n = 7) and 24.6% (n = 16) of the patients reported sensitivity and fatigue of the jaw muscles. In a previous study by Davies, among xerostomic patients with a malignant disease, fewer side effects after gum chewing were reported.[22]

Eighteen patients (27.7%) reported an unpleasant taste of the artificial saliva. Therefore, acceptance of the artificial saliva may be increased, by offering several choices with different tastes. Nausea and diarrhea were also mentioned as side effects of the treatments. However, it is not clear if this should be attributed to the therapy only, since HD treatment itself can also induce these side effects.[31]

CONCLUSION

The results of this crossover study show that in HD patients, chewing gum was preferred for relief of xerostomia over the use of a saliva substitute. However, a subgroup of HD-patients prefers the application of artificial saliva particularly at night. Chewing gum was also rated best on every measurement and could thus play an important role in the palliative care of xerostomia in HD patients.

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8

GENERAL DISCUSSION

ESRD: THE ORAL COMPONENT

In this thesis, we have described studies of consequences of end stage renal disease (ESRD) on several oral parameters. In literature, a high prevalence of bad breath, temporomandibular pain, neglected oral health and reduced oral self-care were reported in ESRD patients.[1-3] Dissecting the exact role of ESRD in oral health, however, has proven to be elusive since paradoxical findings have been reported about the numbers of decayed, missing and filled teeth (DMFT) in hemodialysis patients (HD).[4-6] In order to quantify the role of ESRD, we carried out a cross-sectional study, described in chapter 4. In this analysis, we have compared the oral health status in a cohort of dentate ESRD patients on hemodialysis (HD) or peritoneal dialysis (PD) treatment with a well-defined reference population, matched for age and educational status.

Increased levels of urea and the associated high salivary pH (alkaline), increased calculus formation and remineralization, are characteristic finding in ESRD patients. The consequences of these findings are matter of contention since the net result could potentially have a positive or negative effect on the oral health.[7] The increased salivary pH for example may offer protection of the teeth against acids from bacterial and non-bacterial origin such as gastric acid.[8]

An alternative explanation for our finding of relative good oral health in ESRD patients, could be the increased efficacy, adequacy and improved dialysis treatment modalities during the last decades for patients with ESRD.[9] Since oral and dental foci could jeopardize the success of a renal transplant (NTx),[5] most patients on the waiting list for a renal transplantation underwent a dental examination and treatment before they were included in our study. This could potentially have influenced our results.

Our finding of a relatively normal salivary flow rate in ESRD patients was unexpected, since most studies have reported reduced flow rates in dialysis patients.[8,10-13] Salivary flow rates were shown to be significantly increased during HD sessions (Chapter 2). Previous studies on saliva either used saliva collected before a dialysis session[10,13] or on a non-dialysis day.[8] The variety in collection times in the studies described in literature probably underlies the paradoxical findings in prevalence and severity of hyposalivation in ESRD patients. It can be hypothesized that after completion of the dialysis session, the salivary flow rate gradually will decrease and as a consequence, hyposalivation is present in the post-dialysis episode or interdialytic day. Further studies are warranted to address whether this hypothesis holds true.

THIRST AND XEROSTOMIA

Despite the relative normal salivary flow rates, a large proportion of ESRD patients in our study reported to suffer from thirst (DTI) and xerostomia (XI), which were the major oral related complaints in ESRD patients (Chapters 3 and 6).

Thirst is influenced by many factors including sodium intake, high plasma sodium, potassium depletion, increased levels of angiotensin II, vasopressin, acute increases in plasma urea, psychological factors and feelings of a dry mouth.[14-21] Almost a century ago, Cannon proposed that the first sign of 'normal thirst' is the feeling of dryness in the mouth and throat, and that thirst can be neutralized by drinking water or stimulating salivary flow with fruity acids or chewing gum.[22] In the years thereafter, other investigators have also suggested a relation between reduced salivary flow rates and thirst.[18,23-26] We have shown that oral dryness plays an important role in the fluid intake of HD patients and therefore should receive more attention in the management of fluid intake in ESRD patients.

At the beginning of our studies, no validated thirst questionnaire had been described in the literature. In order to study the clinical impact of thirst in ESRD, we developed the Dialysis Thirst Inventory (DTI), as being described in Chapter 3. The DTI has been used to quantify thirst before, during and after dialysis, thirst at night, during the day and the impact of the fluid restricted diet on the social life.[27] In 2002, Welch published the Thirst Distress Scale (TDS) for dialysis patients with three conceptual definitions: distress, duration and frequency of thirst.[28] At the moment, these two thirst-questionnaires are available to measure thirst in dialysis patients. For validation purposes, it might be considered worthwhile to compare these two thirst-questionnaires in future studies.

Thirst has been associated with an increased concentration of urea in serum.[29] The association between thirst and urea is supported by our results. In the study described in Chapter 2, we have demonstrated that the average urea concentration in saliva (correlating with the concentration in serum) decreases during a HD session, which was accompanied by a reduction in thirst.

Alterations in the composition of saliva in ESRD patients may have contributed to the feeling of dry mouth. Low visco-elastic properties of saliva has, for example, previously been described to result in feelings of a dry mouth.[30] Measuring the visco-elastic properties of saliva from ESRD patients may provide an answer to this hypothesis. Clearly, more investigation is needed to disentangle the role of visco-elastic properties of saliva in thirst in ESRD patients.

The DTI-questionnaire measures subjective aspects of thirst. The underlying mechanism of the increased thirst sensation in ESRD, however, is not clarified by our studies. Several aspects of HD can be hypothesized to be an explanation for our findings, such as physiological and psychological factors.[31,32] Therefore, it is of interest to explore the potential relation between subjective and more objective physiological parameters. Since in both xerostomic and dialysis patients depression is frequently manifest, the role of depression and other psychological

factors influencing water intake in HD patients are a potential explanation for the increased thirst sensation as well.[33-35]

In general, the use of medication is an important cause of xerostomia.[36,37] Amongst the commonly prescribed medications in ESRD patients are anticoagulants, phosphate binders, Ca-antagonists, statines, corticosteroids and vitamins. In general, antihypertensives, which have been shown to cause xerostomia, are used in ESRD patients.[37] In Chapter 3, we have shown, however, that the use of xerogenic medication is not associated with feelings of a dry mouth in ESRD patients.

THIRST AND XEROSTOMIA STRATEGIES

It is important for HD patients to comply to the fluid-restricted, since non-compliance is associated with congestive heart failure and increased mortality. Compliance to the fluid restriction could potentially be enhanced by the reduction of thirst by using chewing gum or artificial saliva. In Chapters 6 and 7, it was demonstrated that both chewing gum and artificial saliva were able to reduce the levels of xerostomia and thirst. In healthy subjects, chewing gum stimulates the salivary flow rate during the first minute with 187%, see Appendix. Most patients preferred using chewing gum, which also appeared to be most effective in the management of thirst and xerostomia in HD patients. However, older patients (> 64 years) mostly preferred the use of spray, see Chapter 7.[38] A few patients complained about the fact that the bottle with artificial saliva was difficult to handle. Therefore it may be considered useful to develop more ergonomic types of bottles, or other means to administer artificial saliva in the oral cavity.[39] The use of chewing gum and artificial saliva did not affect directly the IWG. Nevertheless, several patients reported to postpone water intake probably due to the distracting effect of gum chewing.

The greater part of dialysis patients have developed their own strategy to deal with thirst and the limited fluid intake. Drinking tiny volumes, measuring their daily allowed volume, sucking on sweets, rinsing the mouth, chewing on ice cubs or distraction are amongst the self-care strategies dialysis patients use to reduce their water intake.[40,41] Additional information about the results and effectiveness of the different strategies being described above are therefore of clinical relevance. Finally, the aim is to develop the optimal specific therapeutic regimen for each patient.

POTENTIAL BIAS

Our results could have potentially been biased by several factors. The patients participating in the studies, were recruited from four different centers: two hospital settings (Vrije

Universiteit Medical Center and the Rode Kruis Hospital) and two private dialysis clinics (Dianet Amsterdam and Dianet Utrecht). Although it is possible that the average general health status differs between these centers, we could not demonstrate any statistical significant differences between the four centers for any of our outcome measures.

The dialysis patients from the centers involved were asked to participate in a study about saliva, thirst and oral health. More than half of the patients decided not to participate in this study. Major reasons for non-participation were illness or involvement in other clinical trials. Also, the absence of thirst or oral dryness was reason for non-participation. This could have resulted in an overestimation of the role of thirst and oral dryness in ESRD patients in our study.

Several study designs are described in this thesis: a repeated measurements design (Chapter 2), a cross-sectional design (Chapter 3 and 4), a longitudinal study (Chapter 5) and a crossover design (Chapters 6 and 7). It is not possible to measure the effect of chewing gum and artificial saliva in a double blind, randomized clinical trial. Therefore, we conducted a crossover study (Chapters 6 and 7) with a two-week wash out period, in which no statistically significant crossover effect was found.

Some patients were involved in several parts of the study described in this thesis. Treatment with chewing gum and artificial saliva, for example, could potentially have affected the outcome of xerostomia and thirst in HD patients after two years. Although chewing gum and the saliva substitute were only used for two weeks each, the possibility exists that subjects continued the use of a preferred treatment after completion of the crossover study. Since no longitudinal differences were found, this potential effect is probably not present or too small to detect.

FUTURE RESEARCH

Saliva is presently used for the diagnosis of several systemic diseases, since it is easily collected and contains serum constituents.[42] Analysis of saliva may be useful for the diagnosis of hereditary disorders, autoimmune diseases, malignant and infectious diseases, and endocrine disorders as well as in the assessment of therapeutic levels of drugs and the monitoring of illicit drug use.[42] Maybe, the primary diagnosis of renal failure may also be obtained through saliva since it has recently been shown that uric acid in saliva could be used as a biomarker of renal function.[43] Another potential use of salivary diagnostics may be to monitor the clearance of waste products from the blood during dialysis sessions.

The oral health studies described in Chapters 4 and 5 have focused on general accepted oral health indices. Although these indices have been very useful to describe differences and similarities between patients and healthy subjects, future studies should also include more specific oral health risk factors and oral health related complaints instead of general indices.

Specific problems reported in HD patients are calculus, changes in the periodontal status, dental erosion, oral dryness and level of oral hygiene. Self-reported complaints in ESRD patients include halitosis (bad breath), bad taste and temporomandibular complaints. Special attention for these specific areas may contribute to an increased – oral health related – quality of life of patients with ESRD.

CONCLUDING REMARKS

The aim of this thesis was to provide insight in the role of ESRD on oral dryness, thirst and oral health. In Chapter 2, we revealed that HD treatment has an acute stimulating effect on the salivary flow rate. In Chapter 4, the oral health of dentate ESRD patients was compared with a well-defined reference group. The results indicated that the oral health in our study group was relatively well. The long-term effects of ESRD were discussed in Chapter 5. Renal transplantation had a major effect on the salivary flow rate, xerostomia and thirst, whereas no substantial changes were found for the other oral health variables. Our second aim was to unravel the relationship between thirst, xerostomia, salivary flow rate and IWG. In Chapter 3, we have found that thirst, xerostomia and IWG were statistically significant associated in HD patients, indicating a possible role of oral dryness to explain higher fluid intake between HD sessions.

Saliva stimuli and substitutes might diminish the urge to drink in HD patients, enhancing compliance to the fluid-restricted diet and leading to fewer systemic complications. This potential clinical effect was investigated in Chapters 6 and 7. It was found that chewing gum could reduce thirst and xerostomia in HD patients effectively. Although the net IWG was not affected, chewing gum and artificial saliva could support patients in maintaining their fluid-restricted diet, resulting in better patient outcomes.

To conclude, this thesis describes the interesting research area of oral health in relation to systemic diseases. Increasing awareness of both physicians and dentists for possible relationships and interaction between oral and general health is of major importance and should be encouraged.

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9

SUMMARY

BACKGROUND

The kidneys are essential in removing metabolic waste products, electrolytes and water from the body. End stage renal disease (ESRD) occurs when the function of the kidneys is impaired and reduced towards 5-10% of the original capacity. ESRD patients can receive kidney replacement therapy such as hemodialysis (HD), peritoneal dialysis (PD) or renal transplantation (NTx). During HD and PD treatment, the blood is purified by an extra-corporal artificial kidney (HD) or by means of the peritoneum membrane (PD). Most patients have to maintain a fluid restricted diet since they have no residual urine output and are allowed to drink at maximum 500 mL per day. Since thirst and dry mouth feelings (xerostomia) are among the most frequently occurring symptoms, maintaining this fluid restricted diet can be very difficult resulting in a high interdialytic weight gain (IWG).

Saliva plays an essential role in maintaining an optimal environment in the oral cavity. Several proteins are involved in the anti-viral, anti-fungal and anti-bacterial capacity of saliva. A close relationship exists between the composition of serum and saliva. Therefore, alternations in the amount or composition of saliva could potentially influence the oral health.

The aims of this thesis were:

1) to investigate the acute and long term effects of dialysis treatment on the salivary flow rate, xerostomia, thirst and oral health in ESRD patients.
2) to assess the relationship between oral dryness (reduced salivary flow rates and xerostomia) thirst, and IWG in patients on HD.
3) to investigate potential therapies in order to reduce IWG between dialysis sessions.

SALIVA, ORAL DRYNESS, THIRST AND IWG IN HD PATIENTS

In **Chapter 2,** the acute effects of HD treatment on the flow rate and biochemical composition of saliva were studied. The aim of this study was to evaluate acute effects of HD on the salivary flow rate, pH and biochemical composition before, during and after completion of a dialysis session. In 94 HD patients, unstimulated whole saliva (UWS) and chewing-stimulated whole saliva (CH-SWS) were collected immediately before, during and after a dialysis session. Salivary flow rate, pH, concentration of total protein, albumin, cystatin C and of sodium, potassium and urea were measured. It was revealed that HD treatment had an acute stimulating effect on the salivary flow rate (UWS *before* = 0.30 ± 0.22 mL/min; UWS *during* = 0.39 ± 0.25 mL/min; $P < 0.05$). The mean pH of UWS showed a small but significant increase during hemodialysis (*pH before* = 7.16 ± 0.58 to pH *during* = 7.31 ± 0.49 ; $P < 0.05$). The concentrations of the biochemical constituents (total protein, albumin, cystatin C and S-IgA) in whole saliva were reduced markedly, but no significant differences in output were found. Also the electrolyte concentration did not change during dialysis. The level of urea in CH-SWS declined with 40%

(urea *before* = 25.6 ± 6.4 mmol/L, urea *during* = 15.3 ± 4.5 mmol/L). We concluded that HD has significant acute effects on both salivary secretion rate and protein concentrations in saliva and that the observed decrease in salivary concentrations and proteins are mainly due to an increased watery secretion from the salivary glands.

In **Chapter 3** we described a study to unravel the relationship between oral dryness, fluid-intake and IWG in HD patients. Severe thirst, or the urge to drink, is influenced by many factors such as sodium intake, high plasma sodium, potassium depletion, angiotensin II, vasopressin, acute increase in plasma urea and psychological factors. Thirst can induce non-compliance to this diet, resulting in an increased interdialytic weight gain (IWG = weight predialysis minus postdialysis). Therefore, IWG can be used as an indicator of compliance to the fluid-restricted diet and can be associated with poor patient outcomes such as hypertension, acute pulmonary edema, congestive heart failure, and premature death. Because oral dryness (xerostomia and reduced salivary flow rates) may contribute to experienced thirst, we investigated the possible relation between thirst, salivary flow rate, xerostomia, and IWG in 94 HD patients (64 men, 55 ± 16 years; 30 women, 60 ± 19 years). Unstimulated and chewing stimulated secretion rates of saliva were determined and the level of xerostomia was assessed with a validated Xerostomia Inventory (XI). Thirst was measured with a newly developed Dialysis Thirst Inventory (DTI). It was found that 36% of the patients had hyposalivation (UWS ≤ 0.15 mL/min), before dialysis. The XI scores were positively related with the IWG ($r = 0.25$, $P < 0.001$) and the prevalence and severity of thirst and xerostomia were greater in younger subjects. It was surprisingly that patients *with* urine output did not differ from those *without* urine output with respect to thirst, xerostomia, and IWG. Correlations were found between thirst (DTI) and both IWG and xerostomia (XI) ($r = 0.33$, $P < 0.001$, respectively; $r = 0.74$, $P < 0.001$). Other correlations were observed between xerostomia and both the salivary flow rate and total number of medications ($r = -0.25$, $P < 0.05$, respectively; $r = 0.24$, $P < 0.05$). It was concluded that in HD patients, xerostomia (XI) and thirst (DTI) are associated with a higher IWG. These data provide evidence that, in HD patients, xerostomia is related to both salivary flow rate and thirst (DTI), indicating a possible role of oral dryness to explain higher fluid intake between HD sessions. Since other studies haves shown that saliva stimuli or saliva substitutes could be effective in reducing feelings of a dry mouth, these therapies might also diminish the urge to drink in HD patients, enhancing compliance to the fluid-restricted diet, potentially leading to a decreased IWG.

ESRD AND ORAL HEALTH

At baseline we compared the oral health status of ESRD patients on HD or PD treatment with a matched reference population in a cross-sectional study (**Chapter 4**). Forty-two dentate CRF patients – aged 25-52 years old – were matched with a reference group of 808 dentate

subjects. The oral health was assessed using decayed missing filled (DMF) indices, simplified oral hygiene index (SOHI) and periodontal status. An oral health questionnaire was used to assess self-reported dental problems. It was revealed that all index-scores in the ESRD patients were comparable with the controls except for number of teeth covered with calculus, which was significantly higher ($P < 0.05$) in ESRD patients (4.1 ± 2.6) than in controls (3.0 ± 2.9). The self-reported oral health questionnaire revealed a trend for increased temporomandibular complaints in patients (17% vs 6% in controls; $P = 0.06$) as well as a bad taste (31% vs 7% in controls, $P = 0.08$).

The objective of the longitudinal oral health study, described in **Chapter 5,** was to compare the oral health, salivary flow rates, xerostomia and thirst between ESRD patients remaining on dialysis treatment with those after renal transplantation. At baseline and after two years, oral health, salivary flow rates, xerostomia and thirst were determined in 43 dentate patients. The salivary flow rate of twenty patients who were transplanted increased significantly from UWS = 0.30 ± 0.21 mL/min towards 0.44 ± 0.29 mL/min ($P < 0.001$). The level of xerostomia and thirst decreased while in dialysis patients no differences occurred. After two years, the percentage of bleeding on probing in dialysis patients (n = 23) decreased from 30% till 10%. No further oral health differences were found between dialysis and renal transplant patients. In conclusion, the DMFT, dental plaque, gingival bleeding and periodontal indices did not change remarkable after two years comparing dialysis and renal transplant patients. In dialysis patients awaiting a renal transplant and those who have been transplanted, regular dental examinations are important to prevent oral infections, which could jeopardize the success of a kidney transplant. Furthermore, increased salivary flow rates and reduced levels of both xerostomia and thirst are important aspects and might enhance the oral health related quality of life.

INTERVENTION STUDY

The aim of the randomized two-treatment crossover study, as described in **Chapter 6**, was to investigate the effect of a sugar free chewing gum (Freedent White™) and a xanthan gum-based saliva substitute (Xialine™) on xerostomia, thirst and IWG. HD patients were asked to participate in this study and, finally 65 HD patients (42 men: 55 ± 14 years; 23 women: 55 ± 16 years) participated. After the use of chewing gum or saliva substitute for two weeks, a washout period of two weeks was introduced and hereafter the other regimen was carried out. Xerostomia (XI) and thirst (DTI) were determined at baseline and after each treatment period, as were IWG and salivary flow rates. The level of xerostomia decreased by the use of chewing gum (from XI = 29.9 ± 9.5 to 28.1 ± 9.1, $P < 0.05$). Chewing gum as well as a saliva substitute reduced thirst (DTI) significantly ($P < 0.05$), but no differences occurred for the average IWG or

salivary flow rates. We concluded that the use of chewing gum and, to a lesser extent, a saliva substitute may alleviate thirst and xerostomia in some HD patients.

The second aim of the crossover study was to investigate the effect and preferences of a chewing gum and a artificial saliva in the management of xerostomia in chronic HD patients. Therefore, the more subjective feelings and preferences between the salivary substitute and stimulant were further explored in **Chapter 7**. Artificial saliva was rated statistically significant lower than the chewing gum for effectiveness, taste and global assessment. No preference differences were found for gender and age, although older subjects rated the artificial saliva with higher mark. Thirty-nine subjects (60%) preferred chewing gum and 15% (n = 10) preferred the artificial saliva. Although chewing gum was preferred most, both strategies (chewing gum and artificial saliva) could potentially play an important role in the palliative care of xerostomia in HD patients.

CONCLUDING REMARKS

Dialysis treatment has a direct effect on the composition and amount of saliva. Furthermore, we have shown that both oral dryness and thirst are associated with the amount of fluid consumed between dialysis sessions (IWG). Gum chewing increases the salivary flow rates nearly twofold in healthy subjects. Therefore, we have investigated the effect of the use of chewing gum or artificial saliva on the IWG, oral dryness and thirst, in a group of HD patients. Chewing gum appeared to be the most effective tool to reduce thirst and oral dryness. Especially in older patients, artificial saliva was preferred most. Both chewing gum and artificial saliva should be easily available to assist in maintaining the fluid restricted diet. Besides, it is of major importance to prevent oral infections, which could negatively influence the success of the transplantation. Also after renal transplantation, continued attention for the oral hygiene is of importance to prevent gingival overgrow, due to the use of immunosuppressive medication. We have shown that the salivary secretion rates restored after renal transplantation. This could contribute to the oral-health related quality of life. Finally, daily dialysis treatment at home could potentially contribute in the reduction of oral dryness and thirst.

10

SAMENVATTING

ACHTERGRONDEN

De nieren spelen een essentiële rol bij het verwijderen van metabole afbraakproducten, zouten (elektrolyten) en water uit het lichaam. Wanneer de capaciteit van de nieren gereduceerd is tot 5-10% van de oorspronkelijke capaciteit spreekt men van terminaal nierfalen (ESRD: end stage renal disease). Verschillende nierfunctievervangende therapieën zijn voorhanden zoals hemodialyse (HD), peritoneaal dialyse (PD) of niertransplantatie (NTx). Bij HD behandeling wordt het bloed gezuiverd door een kunstnier. Bij PD behandeling wordt gebruik gemaakt van het buikvlies als filter. Het merendeel van de dialysepatiënten heeft geen restfunctie van de nieren, waardoor geen urine meer kan worden uitgescheiden. De meeste dialysepatiënten volgen daarom een vochtbeperkend dieet, waarbij per dag slechts een halve liter vocht gedronken mag worden. Bovendien heeft het overgrote deel van de dialysepatiënten te maken met zowel dorst als monddroogte. Het is daarom goed voor te stellen dat het voortdurend houden van een vochtbeperkend dieet bijzonder lastig kan zijn.

Speeksel speelt, naast het bevochtigen van de mond, een belangrijke rol bij het handhaven van een optimaal, beschermend mondmilieu. Diverse eiwitten in het speeksel dragen bij aan de antivirale, antischimmel en antibacteriële eigenschappen. Aangezien een nauwe relatie bestaat tussen de samenstelling van bloed (serum) en speeksel, valt het te verwachten dat veranderingen in samenstelling van invloed kunnen zijn op de mondgezondheid.

Het in dit proefschrift beschreven onderzoek heeft de volgende doelstellingen:

1) het onderzoeken van acute en lange termijn effecten van dialyse (zowel HD als PD) op speeksel, xerostomie, dorst en mondgezondheid bij patiënten met terminaal nierfalen.
2) het bepalen van de relatie tussen monddroogte, dorst en interdialytische gewichtstoename (IWG) in hemodialyse patiënten.
3) het onderzoeken van mogelijke therapieën die het IWG, de dorst en de monddroogte kunnen reduceren.

SPEEKSEL, MONDDROOGTE, DORST EN IWG IN HD PATIËNTEN

In **hoofdstuk 2** zijn de acute effecten van hemodialyse behandeling op speekselsecretiesnelheid en biochemische samenstelling nader beschreven. Het doel van het onderzoek was om het effect van hemodialyseren (*vóór*, *tijdens* en *na* dialyse) op de secretiesnelheid, de zuurgraad (pH) en biochemische samenstelling van speeksel te onderzoeken. Ongestimuleerd speeksel (UWS = unstimulated whole saliva) en kauw-gestimuleerd speeksel (CH-SWS = Chewing stimulated whole saliva) werden *vóór*, *tijdens* en *na* de dialyse verzameld. Vervolgens werd de secretiesnelheid, pH, concentratie van totaal eiwit, albumine, cystatine C en S-IgA bepaald. Daarnaast werden de concentraties van natrium, kalium en ureum in speeksel gemeten.

Hemodialysebehandeling had een direct effect op de secretiesnelheid (UWS *vóór* = 0,30 ± 0,22 ml/min; UWS *tijdens* = 0,39 ± 0,25 ml/min; $P < 0,05$). De gemiddelde pH van ongestimuleerd speeksel steeg licht tijdens de dialyse, van pH = 7,16 ± 0,58 (*vóór* dialyse) tot pH = 7,31 ± 0,49 (*tijdens* dialyse; $P < 0,05$). De concentratie van zowel totaal eiwit, albumine, cystatine C, S-IgA als het zoutgehalte (elektrolyten) in speeksel daalde ten gevolge van de dialyse. Echter, de uitscheiding per minuut (= output) bleef gelijk. De concentratie ureum in speeksel (CH-SWS) nam tijdens de dialyse af met maar liefst 40% (ureum *vóór* = 25,6 ± 6,4 mmol/l; ureum *tijdens* = 15,3 ± 4.5 mmol/l). Hemodialysebehandeling heeft dus een direct effect op zowel de secretiesnelheid als de eiwitconcentraties van speeksel. Zeer waarschijnlijk zijn de gevonden concentratieverschillen in het bijzonder veroorzaakt door een toegenomen waterige secretie uit de speekselklieren.

In **hoofdstuk 3** wordt de relatie tussen speeksel, monddroogte, dorst en IWG in HD patiënten beschreven. Dorst of 'de behoefte om te drinken' wordt beïnvloed door allerlei factoren zoals zoutinname, een hoge zoutconcentratie in het bloed, kalium, angiotensine II en vasopressine. Bovendien spelen, naast een snelle toename van de hoeveelheid ureum in het bloed, psychologische factoren een rol. Dorst kan, bij patiënten zonder restfunctie (= urine productie), van invloed zijn op het niet volgen van een vochtbeperkend dieet. Dit kan uiteindelijk leiden tot een toename in IWG. Grote interdialytische gewichtsverschillen gedurende langere tijd kunnen gepaard gaan met een hoge bloeddruk, hartfalen en vroegtijdig overlijden.

Verminderde speekselsecretie en monddroogte spelen mogelijk een rol bij het dorstgevoel. Daarom werd de relatie tussen dorst, monddroogte en IWG onderzocht bij 94 HD patiënten (64 mannen: 54,8 ± 15,5 jaar; 30 vrouwen: 59,5 ± 18,7 jaar). Zowel UWS als CH-SWS werd opgevangen. De mate van monddroogte werd bepaald met behulp van een gevalideerde 'xerostomie vragenlijst' (XI). Tot slot werd de mate van dorst gemeten met een nieuw ontwikkeld instrument, de zogenaamde 'dialyse- en dorstvragenlijst' (DTI). Voor aanvang van de dialyse was bij 36% van de patiënten sprake van hyposalivatie (UWS ≤ 0.15 ml/min). Bovendien werd gevonden dat de mate van monddroogte (XI) samenhangt met de hoeveelheid vocht die men tussen de dialyses tot zich nam ($r = 0,25$, $P < 0,001$). Patiënten jonger dan 65 jaar rapporteerden meer monddroogte en dorst dan ouderen. Een opmerkelijke bevinding was dat de mate van dorst (DTI), monddroogte en IWG gelijk was bij patiënten *met* restfunctie en degene *zonder* restfunctie. Dorst (DTI), IWG en monddroogte (XI) hingen nauw met elkaar samen (DTI en IWG: $r = 0,33$, $P < 0,001$; DTI en XI: $r = 0,74$, $P < 0,001$). Daarnaast werd een statistisch significant verband gevonden tussen de mate van monddroogte, de speekselsecretiesnelheid ($r = -0,252$, $P < 0,05$) en het totale aantal gebruikte medicijnen ($r = 0,235$, $P < 0,05$). Dat een toename in de mate van monddroogte of dorst bij HD patiënten gepaard gaat met een hogere IWG, suggereert dat monddroogte mogelijk een rol speelt bij de behoefte – tussen de dialyses door – vocht tot zich te nemen.

Eerder onderzoek heeft aangetoond dat bevochtiging van de mond, door kauwgom of kunstspeeksel, effectief werkt tegen monddroogte. Daarnaast zouden deze interventies mogelijk als therapie bij HD patiënten kunnen worden toegepast, om de behoefte om te drinken te verminderen. Hierdoor zou men zich beter kunnen houden aan het vochtbeperkend dieet, hetgeen uiteindelijk zou kunnen leiden tot een verlaging van de IWG.

NIERFALEN EN MONDGEZONDHEID

De mondgezondheid van HD en PD patiënten werd in een cross-sectioneel onderzoek vergeleken met een controlegroep (**hoofdstuk 4)**. Tweeënveertig dentate (= eigen tanden en kiezen) patiënten met terminaal nierfalen werden vergeleken met een op leeftijd en opleiding overeenkomende controle groep tussen de 25-52 jaar, (n = 808). Het aantal vervallen (D), verloren (M) en gevulde (F) gebitselementen (DMFT) werd vastgelegd. Tevens werd de mate van mondhygiëne en de conditie van het tandvlees bepaald. Met behulp van een mondgezondheidsvragenlijst werden aanvullende gegevens over eventuele gebitsproblemen vastgelegd. De mondgezondheid van ESRD patiënten bleek vergelijkbaar met die van de controlegroep. Alleen het aantal gebitselementen met tandsteen was in de patiëntengroep hoger (4,1 ± 2,6) dan in de controlegroep (3,0 ± 2,9, $P < 0,05$). Zeer waarschijnlijk hangt dit samen met de verhoogde concentratie ureum in het speeksel, hetgeen leidt tot een hogere pH in de mond en het neerslaan van speekselzouten op de gebitselementen. Uit de mondgezondheidsvragenlijst bleek dat het aantal ESRD patiënten met kaakgewrichtsklachten (16,7%) groter was dan in de controlegroep (5,7%; $P = 0,06$). Daarnaast rapporteerden ERSD patiënten vaker een slechte smaak (31,0%) dan de controlepatiënten (6,8%; $P = 0,08$). Ook dit hangt mogelijk samen met een verhoogde concentratie ureum in speeksel, dat onder invloed van bacteriën omgezet kan worden in ammoniak.

De longitudinale veranderingen in de mondgezondheid bij ESRD patiënten zijn beschreven in **hoofdstuk 5**. Doel van dit onderzoek was om gedurende twee jaar de mondgezondheid, speekselsecretiesnelheid, mate van xerostomie (XI) en dorst (DTI) van dialyserende ESRD patiënten te vergelijken met een groep patiënten die in dezelfde periode waren getransplanteerd. Bij aanvang van het onderzoek werd de mondgezondheid, speekselsecretiesnelheid, mate van monddroogte (XI) en dorst (DTI) vastgesteld bij 43 dentate patiënten. Het aantal DMFT, de hoeveelheid tandplaque, en de conditie van het tandvlees verschilden niet tussen beide groepen. De ongestimuleerde speekselvloed (UWS) van twintig getransplanteerde patiënten steeg van 0,30 ± 0,21 ml/min naar 0,44 ± 0,29 ml/min, $P < 0,001$. De mate van monddroogte en dorst daalde in deze groep, terwijl bij de dialysepatiënten geen verschil optrad. Het aantal gebitselementen met bloeding na sonderen daalde in een periode van twee jaar, van 29,5% naar 10,3% in de groep dialysepatiënten (n = 23). Verder werden geen andere verschillen in de mond geconstateerd tussen de dialysegroep en de getransplanteerde

patiënten. Blijvende tandheelkundige begeleiding, van zowel dialysepatiënten op de wachtlijst voor een niertransplantie als reeds getransplanteerde patiënten, is van eminent belang om orale ontstekingen te voorkomen. Daarnaast spelen een toegenomen hoeveelheid speeksel en verminderde monddroogte een belangrijke rol bij een verbeterde kwaliteit van het leven in getransplanteerde patiënten.

INTERVENTIE STUDIE

Het doel van de cross-over studie beschreven in **hoofdstuk 6**, was het effect van kauwgom en kunstspeeksel (spray) op dorst (DTI), monddroogte (XI) en IWG bij HD patiënten te onderzoeken. Vijfenzestig HD patiënten (42 mannen: 55 ± 14 jaar; 23 vrouwen: 55 ± 16 jaar) deden mee aan dit onderzoek. De patiënten werden willekeurig in een groep ingedeeld om gedurende twee weken kauwgom (suikervrije Freedent White™) of kunstspeeksel (Xialine™) te gebruiken. Na twee weken kauwen of sprayen, werd gedurende twee weken geen therapie gegeven, zodat het effect van de ene therapie op de andere geminimaliseerd werd. Vervolgens kreeg de eerste groep kunstspeeksel en de andere groep kauwgom aangeboden. De mate van monddroogte (XI), dorst (DTI) en IWG werden vóór en na iedere behandelperiode bepaald. De mate van monddroogte daalde door het kauwgomgebruik van XI = 29,9 ± 9,5 tot XI = 28,1 ± 9,1 ($P < 0,05$). Zowel kauwgom als kunstspeeksel gaf een significante verlaging van het dorstgevoel ($P < 0,05$). De gemiddelde ongestimuleerde speekselsecretiesnelheid en de gemiddelde IWG veranderden echter niet. Geconcludeerd werd dat het gebruik van kauwgom en – in mindere mate – kunstspeeksel zowel dorst als monddroogte kunnen verminderen bij HD patiënten.

Het tweede doel van de cross-over studie was het effect van en de voorkeur voor kauwgom of kunstspeeksel bij de behandeling van xerostomie nader te onderzoeken. De resultaten van het vragenlijstonderzoek naar voorkeur en beleving van kauwgom en mondspray zijn beschreven in **hoofdstuk 7**. Voor zowel de effectiviteit, smaak als de totaalbeoordeling werd kunstspeeksel significant lager beoordeeld dan kauwgom. Geslacht en leeftijd hadden geen effect op de voorkeur. Oudere onderzoeksdeelnemers beoordeelden kunstspeeksel wel met een hoger gemiddeld eindcijfer. Zestig procent van de mensen (n = 39) gaf de voorkeur aan kauwgom en vijftien procent (n = 10) gebruikte liever kunstspeeksel bij het verlichten van monddroogte. Hoewel kauwgom de voorkeur genoot kunnen beide strategieën, afzonderlijk of in combinatie, een belangrijke rol spelen bij de palliatieve behandeling van monddroogte in HD patiënten.

CONCLUDERENDE OPMERKINGEN

Dialyseren heeft een direct effect op de samenstelling en hoeveelheid speeksel. Daarnaast hebben wij aangetoond dat zowel monddroogte als dorst samenhangen met de hoeveelheid vocht die tussen de dialyses wordt geconsumeerd (IWG). Het kauwen op kauwgom kan de speekselsecretiesnelheid bijna doen verdubbelen bij gezonde personen. Daarom werd in een groep HD patiënten onderzocht wat het effect van kauwgom en kunstspeeksel was op het IWG, de monddroogte en het dorstgevoel. De deelnemers aan het onderzoek vonden het gebruik van kauwgom het meest effectieve middel om dorst en droogte te verminderen. Vooral oudere patiënten hadden ook baat bij het gebruik van kunstspeeksel. Deze therapieën zouden voor alle dialysepatiënten voorhanden moeten zijn, zodat het houden van een vochtbeperkend dieet dragelijker en gemakkelijker zou kunnen worden. Daarnaast is het van belang de mond van dialysepatiënten ontstekingsvrij te houden in verband met het slagen van een eventuele niertransplantatie. Ook na de transplantatie is blijvende aandacht voor de mondhygiëne van belang om de kans op gingivale overgroei door het gebruik van immunosupresiva te verminderen. Uit ons onderzoek bleek tevens dat de hoeveelheid speeksel na transplantatie volledig genormaliseerd was, wat mogelijk een positieve bijdrage kan leveren aan de mondgezondheid gerelateerde kwaliteit van het leven. Tot slot zou de steeds vaker toegepaste (dagelijkse) HD thuisdialyse mogelijk een belangrijke bijdrage kunnen leveren aan een vermindering van monddroogte en dorst.

APPENDIX

PREFERENCES AND SALIVA STIMULATION OF EIGHT DIFFERENT CHEWING GUMS

Casper P. Bots, Henk S. Brand, Enno C.I. Veerman, Barbara M. van Amerongen, Arie V. Nieuw Amerongen

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ABSTRACT

Objectives

Chewing gums have been studied for clinical use to stimulate the salivary flow rate in healthy and diseased individuals. However, differences in preferences of chewing gums may influence patient compliance during long-term use. Therefore, we compared the effect of several chewing gums on the flow rate of whole saliva and pH, and investigated the preferences of these gums.

Material and methods

Eighty-three healthy subjects participated in the first part of the study. Both parafilm-stimulated and chewing gum-stimulated whole saliva from eight different chewing gums was collected and salivary flow rate and pH were determined. In another group of 112 healthy subjects, we investigated the preferences for the chewing gums with a 10-item questionnaire.

Results

All gums had comparable effects on salivary flow rate and pH. The average increase in flow rate was 187% during the first minute of chewing compared with parafilm stimulation. After 10 minutes of gum chewing, the amount of saliva was equal to parafilm stimulation. The questionnaire showed differences in preferences for the chewing gums, which were related to taste and gum shape. Gender interactions were observed for sparkling taste ($P = 0.019$), global assessment ($P = 0.047$) and the willingness to use the gum for several weeks ($P = 0.037$).

Conclusions

Although all chewing gums stimulated the salivary flow rate equally, the observed differences in preferences may influence long-term compliance. Therefore, we recommend that chewing gums are tested before the start of clinical studies, to identify the most appreciated chewing gum for specific groups of patients.

INTRODUCTION

Salivary gland hypofunction, which results in reduced salivary flow rates, is often caused by medication.[1] It has also been observed in patients who received head and neck radiotherapy,[2] those on hemodialysis[3,4] and in those with autoimmune disorders e.g. Sjögren's syndrome.[5] To some extent, oral dryness and related complaints can be relieved by saliva substitutes and saliva stimulants, such as lozenges and chewing gum.[6,7,8,9,10]

Chewing gum and lozenges both stimulate the activity of the salivary glands and as a consequence the salivary flow rate in healthy and most diseased individuals.[10,11] In contrast, saliva substitutes provide a passive moistening of the oral tissues. Almost 69% of patients with advanced cancer preferred gum to artificial saliva for the management of xerostomia,[9] or the feeling of having a dry mouth.[12,13] Limited daily use of chewing gum for eight weeks elevated the unstimulated salivary flow rate by 16% in healthy subjects. After termination of the experiment, the salivary flow rate remained elevated for an additional two months.[14] Also xerostomia patients with salivary hypofunction had persistent increased flow rates after eight weeks stimulation by chewing gum.[6,15]

Although different chewing gums produced only slight differences between saliva secretion rate and pH,[16] varying patient group preferences have been reported for saliva stimulants such as chewing gum and lozenges.[9,17] Because such differences may influence patient compliance during long-term clinical studies with saliva stimulants, we compared the effect of several chewing gums on the salivary flow rate and pH and investigated differences in preferences for these saliva stimulants.

MATERIALS AND METHODS

Participants

Eighty-three dental students (41 men: 25.6 ± 4.2 years; 42 women: 24.1 ± 3.2 years) participated in the first part of the study. None of the students were using medication, except for the use of oral contraceptives in most women. Pregnant women were excluded from the study. The procedures were approved by the Medical Ethical Committee of the Vrije Universiteit Medical Center, Amsterdam, the Netherlands.

Saliva collection

Subjects were instructed to abstain from smoking, drinking and eating one hour before saliva was collected. Saliva was collected by means of the "spitting method".[18] Sampling took place at room temperature between 8.30 and 10.30 AM. Before collection, participants were asked to rinse their mouth with water. After a 15 minutes break, before the collection started, the subjects were instructed to void the mouth of saliva by swallowing. Mechanically stimulated

Table 1. Characteristics of the eight chewing gums investigated

	Name	Shape	Weight (g)	Manufacturer
WF-S	Orbit Winterfresh	Stick	2.7	A
WF-T	Extra Winterfresh	Tab	2.0	A
WF-P	Freedent Winterfresh	Pellet	1.5	A
PM-S	Orbit Peppermint	Stick	2.7	A
PM-T	Extra Peppermint	Tab	2.0	A
PM-P	Freedent Peppermint	Pellet	1.5	A
SM-P	Freedent Sweetmint	Pellet	1.5	A
LO-P	Liquorice Original	Pellet	1.3	B

A = Wm. Wrigley Jr. Company (USA), B = Stimorol Dandy A/S (Denmark)

saliva was collected during five minutes using a 5 x 5 cm flat piece of tasteless wax (Parafilm "M", American National CAL, Chicago, USA). During the saliva collection period, the saliva was spitted out in a pre-weighed test tube every 30 seconds. After another 15 minutes pause, each participant received randomly a piece of one of the chewing gums (for characteristics of the eight sugar-free chewing gums, see Table 1). The participants were allowed to chew at their own natural pace.[19] Stimulated whole saliva was collected at intervals of 0-1, 1-2, 4-5 and 9-10 min after the start of chewing. The volume of saliva was determined gravimetrically (assuming 1 g = 1 mL) and the pH was measured within five minutes after saliva collection (Sentron pH-system 1001, Roden, The Netherlands).

Study design and questionnaire

To identify which chewing gum was preferred, another group of 112 dental students (61 men: 23.2 ± 4.1 years; 51 women: 24.1 ± 3.2 years) participated in the second part of the study. After a uniform instruction to use the gum freely during the next two days, the subjects randomly received one package of chewing gum (see Table 1). At the third day, a taste-questionnaire with 10 items was completed. The preferences for the different chewing gums were measured with several 100mm visual analogue scales (VAS) (see Table 2). Next, the volunteers randomly received a package of another chewing gum. This way, each individual tested three of the eight different chewing gums.

Statistical methods

The statistical analyses were carried out using SPSS (version 10.0, SPSS Inc., Chicago, IL, USA). First, we assessed the overall effect of the chewing gums on salivary flow rate and pH with repeated-measures multivariate analysis of variance (MANOVA). Next, we investigated the effect of each individual chewing gum on salivary flow rates and pH with the General Linear Model of ANOVA using a repeated measures design, followed by paired *t*-tests as *post-hoc* procedure.

Differences in preferences for the gums were analyzed with ANOVA, followed by Tukey multiple comparison tests when appropriate. Effects of gum taste and gum size (see Table 1) and

Table 2. Chewing gum questionnaire

1.	How many pieces of chewing gum did you use?	
2.	On average, how many minutes did you chew on one piece of gum?	
3.	Consistency	VAS (soft – firm)
4.	Stickiness	VAS (sticky – not sticky)
5.	Taste I	VAS (unpleasant – pleasant)
	Taste II	VAS (flat – fresh)
	Taste III	VAS (nasty – delicious)
	Taste IV	VAS (mild – strong)
6.	How long does the gum maintain its taste?	VAS (short – long)
7.	What was the stimulated saliva like?	VAS (watery – slimy)
8.	For how many weeks would you be willing to chew this gum, six times a day?	
9.	Which overall score would you give this gum	(1 – 10)
10.	Other comments	

the potential interaction between chewing gum and gender were explored with multivariate analysis of variance (MANOVA) followed by LSD pairwise comparisons when appropriate. All levels of significance were set at $P < 0.05$.

RESULTS

We investigated the potential effects of eight different chewing gums on the salivary flow rate and pH. MANOVA showed no statistical significant differences between the tested chewing gums with regard to the salivary flow rate, presented in Figure 1 and Table 3. All chewing

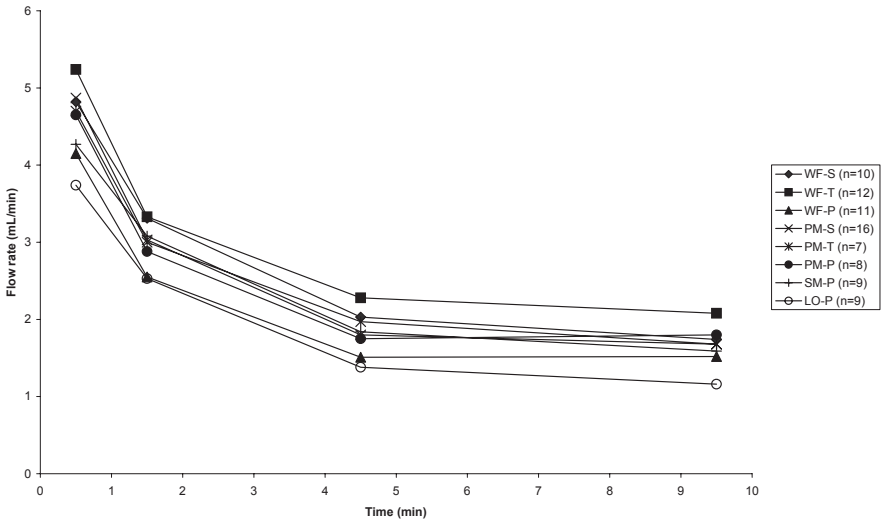

Figure 1. Mean secretion rates of chewing gum stimulated saliva at different time points (n = 7 – 16). (Error bars have been omitted for clarity)

Table 3. Secretion rates of chewing gum stimulated saliva at different time points, compared to parafilm stimulated saliva

Chewing gum gum	n	Parafilm stimulated (mL/min)	Chewing gum stimulated (mL/min)			
			0-1 min	1-2 min	4-5 min	9-10 min
WF-S*	10	1.57 ± 0.75	4.82 ± 1.30§	3.31 ± 0.71§	2.03 ± 0.46	1.74 ± 0.61
WF-T*	12	1.66 ± 0.48	5.24 ± 1.08§	3.33 ± 0.65§	2.28 ± 0.68#	2.08 ± 0.53#
WF-P*	11	1.58 ± 0.78	4.15 ± 1.48#	2.55 ± 0.81§	1.51 ± 0.65	1.52 ± 0.78
PM-S*	16	1.60 ± 0.49	4.87 ± 1.32§	3.03 ± 1.09§	1.80 ± 0.56	1.68 ± 0.59
PM-T*	7	1.43 ± 0.60	4.70 ± 0.84#	3.00 ± 0.81#	1.97 ± 0.67	1.68 ± 0.57
PM-P*	8	1.55 ± 0.33	4.65 ± 1.10#	2.88 ± 0.76	1.75 ± 0.58	1.80 ± 0.83
SM-P*	9	1.98 ± 0.56	4.27 ± 1.05§	3.08 ± 1.09	1.84 ± 0.60	1.59 ± 0.65
LO-P*	9	1.44 ± 0.61	3.74 ± 1.07#	2.53 ± 0.50#	1.38 ± 0.37	1.16 ± 0.52

Data are expressed as mean ± SD (n = 7-16). General Linear Model of ANOVA using a repeated measures design: * $P < 0.05$. Paired *t*-test vs parafilm stimulated saliva: § $P < 0.01$, # $P < 0.05$

Table 4. pH of chewing gum stimulated saliva at different time points, compared with the pH of parafilm stimulation

Chewing gum	n	Parafilm stimulated	Chewing gum stimulated			
			0-1 min	1-2 min	4-5 min	9-10 min
WF-S	10	7.2 ± 0.4	7.4 ± 0.1	7.4 ± 0.2	7.7 ± 0.4	7.7 ± 0.3
WF-T*	12	7.1 ± 0.2	7.3 ± 0.2	7.5 ± 0.2#	7.6 ± 0.2§	7.6 ± 0.2§
WF-P	11	7.2 ± 0.3	7.3 ± 0.2	7.5 ± 0.3	7.7 ± 0.3	7.7 ± 0.3
PM-S*	16	7.3 ± 0.2	7.4 ± 0.2	7.6 ± 0.2#	7.8 ± 0.2§	7.7 ± 0.3§
PM-T	7	7.1 ± 0.1	7.4 ± 0.2	7.5 ± 0.1	7.5 ± 0.1	7.6 ± 0.1
PM-P	8	7.2 ± 0.1	7.4 ± 0.2	7.7 ± 0.3	7.8 ± 0.4	7.9 ± 0.4
SM-P*	9	7.1 ± 0.2	7.3 ± 0.1	7.5 ± 0.2	7.7 ± 0.3#	7.7 ± 0.3
LO-P	9	7.1 ± 0.3	7.4 ± 0.3	7.5 ± 0.2	7.7 ± 0.3	7.6 ± 0.3

Data are expressed as mean ± SD (n = 7-16)

General Linear Model of ANOVA using a repeated measures design: * $P < 0.05$

Paired *t*-test vs pH of parafilm stimulated saliva: § $P < 0.01$, # $P < 0.05$

gums stimulated the flow rate significantly during the first minute of chewing, compared with parafilm stimulation. The average increase was on average 187% (range 116 to 228%). Most chewing gums showed a sustained increase in flow rate during the second minute (average 86%, range 56 to 111%). After 10 minutes of gum chewing, the amount of saliva was equal to the saliva stimulation by tasteless parafilm.

The data on salivary pH are presented in Table 4. MANOVA demonstrated no statistical significant differences between the chewing gums with regard to the pH. The salivary pH showed a small increase during the period of 10 minutes chewing. This increase in pH, however, only reached statistical significance for WF-T, PM-S and SM-P.

To identify which chewing gum had the highest preference, we tested the chewing gums in a crossover study in another group of 112 subjects. Each subject tested three different chewing gums during two days and was asked to complete a chewing gum questionnaire for each gum. In total 306 questionnaires were returned, representing a response rate of 91%.

Table 5. Use and preferences for eight different chewing gums

Chewing gum	n	Pieces consumed*	Minutes chewed*	Consistency* (soft - firm)	Taste I* (unpleasant - pleasant)	Taste II* (flat - fresh)	Taste III* (nasty - delicious)	Global assessment* (1–10)
WF-S	47	4.9 ± 2.4	35.5 ± 30.3	5.0 ± 2.8	3.9 ± 2.6	5.1 ± 2.3	4.5 ± 2.4	5.7 ± 1.6
		(a)	*(a)*	*(a,b)*	*(a)*	*(a,b,c)*	*(a)*	*(a)*
WF-T	39	4.9 ± 2.1	26.8 ± 20.3	5.1 ± 2.8	4.9 ± 2.8	4.9 ± 2.4	5.3 ± 2.8	6.2 ± 1.6
		(a,b)	*(a)*	*(a,b)*	*(a,b)*	*(a,b)*	*(a,b,c)*	*(a,b)*
WF-P	26	7.1 ± 2.9	27.0 ± 16.5	5.0 ± 2.0	6.0 ± 2.2	5.6 ± 1.9	6.0 ± 2.2	6.7 ± 1.4
		(b,c)	*(b)*	*(a)*	*(a,b,c)*	*(a,b,c)*	*(a,b,c)*	*(a,b)*
PM-S	36	6.1 ± 1.3	48.3 ± 38.3	4.1 ± 2.6	6.6 ± 2.5	5.2 ± 1.8	6.2 ± 2.5	7.2 ± 1.4
		(b,c)	*(b)*	*(a)*	*(b,c,d)*	*(a,b,c)*	*(b,c,d)*	*(b,c,d)*
PM-T	47	5.2 ± 1.6	35.7 ± 23.6	5.0 ± 2.4	5.9 ± 2.4	4.4 ± 1.9	5.9 ± 2.4	6.6 ± 1.4
		(a,b)	*(a)*	*(a,b)*	*(b,c,d)*	*(a)*	*(b,c)*	*(b,d)*
PM-P	53	6.6 ± 2.8	33.6 ± 25.0	5.2 ± 2.4	6.0 ± 2.6	6.0 ± 2.3	5.8 ± 2.5	6.6 ± 1.5
		(b,c)	*(a)*	*(b)*	*(b,c,d)*	*(b,c)*	*(a,b,c)*	*(b,d)*
SM-P	23	7.0 ± 2.6	31.2 ± 31.0	5.0 ± 1.9	6.7 ± 2.5	5.1 ± 2.1	7.1 ± 1.8	7.2 ± 1.2
		(b,c)	*(a)*	*(a,b)*	*(b,c,d)*	*(a,b,c)*	*(b,c,d)*	*(b,c,d)*
LO-P	35	6.7 ± 3.5	26.9 ± 21.5	4.7 ± 2.3	4.9 ± 3.3	4.8 ± 2.1	5.2 ± 2.9	5.8 ± 2.1
		(b,c)	*(a)*	*(a,b)*	*(a,b)*	*(b,c,d)*	*(a,b)*	*(a)*

Data are expressed as mean ± SD. * ANOVA $P < 0.05$, followed by Tukey multiple comparison tests. Chewing gums sharing **a common character** *(a, b, c or d)* **in a vertical column** do **not differ significantly** with regard to that item of the questionnaire. Only items from the questionnaire which showed significant statistical differences are included in the Table.

The results from the questionnaire revealed statistical significant differences in use and preferences for the chewing gums (Table 5).

A significant difference was observed for the average time the subjects chewed on a gum. The PM-S gum was used longer than any other gum, whereas the WF-T was used shortest. The global assessment showed that the subjects preferred the PM-S and SM-P gums significantly to the WF-S and LO-P gum. This preference is also demonstrated by the high scores of PM-S and SM-P with regard to Taste I (unpleasant – pleasant) and Taste III (nasty – delicious), in contrast to the low scores of WF-S and LO-P on these VAS scales.

With the use of MANOVA, we compared the overall differences between peppermint flavored gums (PM-S, PM-T and PM-P) and Winterfresh chewing gums (WF-S, WF-T and WF-P). This revealed that the PM gums were considered more pleasant than the WF gums (Taste I = 6.1 ± 2.5 and 4.7 ± 2.7, respectively, $P < 0.001$) and more delicious (Taste III = 5.9 ± 2.4 and 5.1 ± 2.5, respectively, $P = 0.010$). Also the global assessment of the PM gums (6.7 ± 1.4) was significantly higher than that of WF gums (6.1 ± 1.6, $P = 0.001$). The subjects chewed significantly longer on PM than on WF gum (38.5 ± 29.7 vs 29.8 ± 24.4 minutes, $P = 0.012$) and were willing to use this gum six times a day for a longer period of time (2.8 ± 2.7 vs 2.0 ± 2.4 weeks, $P = 0.014$).

Potential effects of the shape of the gums were also explored with MANOVA. This showed that the pellet-shaped gums (PM-P and WF-P) were consumed significantly more (6.7 ± 2.9 pieces consumed, $P < 0.001$) than stick or tab-shaped gums (stick-shaped: 5.4 ± 2.1; tab-shaped: 5.1 ± 2.0). The subjects chewed significantly longer on the stick-shaped gums (41.1 ± 34.3 minutes, $P = 0.013$) than on the tab or pellet-shaped gums (30.9 ± 22.5 and 30.7 ± 24.8 minutes, respectively). The taste of the pellet-shaped gums was considered more fresh (Taste II: 5.4 ± 2.2, $P = 0.039$) than that of stick or tab-shaped gums (5.1 ± 2.1 and 4.6 ± 2.1, respectively). Saliva produced by chewing pellet-shaped gums was considered more slimy (3.5 ± 1.8, $P = 0.049$) than that produced by sticks or tabs (2.9 ± 1.9 and 3.1 ± 1.9, respectively).

A statistical significant gender interaction was revealed for Taste II (dull – sparkle, $P = 0.019$). Women considered the WF-S more sparkling than male subjects, while the opposite was observed for WF-P. A gender interaction was also seen for the global assessment ($P = 0.047$): male subjects appreciated WF-P more, whereas the SM-P was preferred more by women. Finally, a gender interaction was shown for the number of weeks that the subjects were willing to use a gum ($P = 0.037$). Men expressed that they were willing to use PM-S for a longer time, whereas women reported longer times for WF-P.

DISCUSSION

In this study, we compared eight different sugar-free chewing gums with regard to effects on the salivary flow rate, pH and differences in preferences. All investigated gums stimulated the salivary flow rate significantly during the first minute, followed by a progressive decline of the flow rate (Figure 1 and Table 3).

A positive relation between the weight of the chewing gum and the salivary flow rate has been reported.[11] In our study, no significant differences in stimulating salivary flow rates were observed between the gums, which differed in weight from 1.3 to 2.7 gram (see Table 1). This result is in agreement with a previous study on other gums,[16] and suggests that the stimulation of the flow rate by chewing gum is not related to differences in gum taste, size, shape or weight.

The initial increase in flow rate is probably induced by a gustatory stimulus by the chewing gums. Within 39 seconds, the intensity of taste showed a peak value.[20] Therefore, the observed decline in flow rate during the continued chewing of the gum could be related to loss of flavour. However, during chewing a gum also softens and reduces in size.[11] This might lead to a reduced stimulation of periodontal mechanoreceptors,[21] which may also contribute to the decrease in flow rate.

When the subjects used the chewing gums freely, the average chewing time for each piece of gum was 33 minutes, which is comparable with the mean value for the U.S. population (36 minutes).[22] Between the various gums, however, significant differences in chewing time

were observed, as well as in the willingness to use it for several weeks. These differences seem to be related to both taste and size. The mean chewing time and the willingness to use were significantly higher for peppermint-flavoured gums (PM), which were also rated more pleasant than the winterfresh (WF) gums. The subjects also used the larger stick-shaped gums longer than the smaller tab or pellet-shaped gums. As a result, the chewing gum that combines peppermint taste with a stick shape (PM-S) was used longer than any of the other gums (Table 5).

The questionnaire revealed significant gender effects for several taste items as well as for the willingness to use chewing gum for several weeks. This gender effect on taste preferences seems at variance with other studies, reporting no gender differences in taste perception of sweetness[23,24] and threshold sensitivity to basic tastes.[25] The gender effect in the present study was not related to the different gustatory thresholds of pregnant women,[26] since these were excluded from the study.

Several investigators suggested the clinical use of chewing gums for the relief of patients with xerostomia or hyposalivation.[6,7,9,10,15] Although all chewing gums investigated in our study stimulated the salivary flow rate equally, the observed differences in preferences probably may influence compliance during long-term use. Therefore, factors like taste, shape and size should be taken into account in the design of clinical studies, which investigate the effect of chewing gums in specific groups of patients.

In real life, most people will use several different brands of chewing gums. The results of this study apply to patient cohorts whose gum use is supervised. In addition, the selected criteria (flow rate and pH) represent just two of a multitude of biological parameters that could be used to rank chewing gums for potential use in patients with xerostomia.

Our study has been limited to dental students without systemic diseases, having a good oral health and normal salivary flow rates.[27] An altered taste has been reported in elder individuals,[25] patients with reduced salivary flow rates,[28] diabetics,[29] and in patients on hemodialysis.[30] This might have influenced the preferences for the chewing gums. Taste preferences may also vary among populations due to environmental, behavioural, demographic and other reasons. Therefore, we recommend that the preferences for chewing gums are tested in patients before the start of long-term clinical studies, in order to identify the most appreciated chewing gum for each specific group of patients and to get optimal patient compliance.

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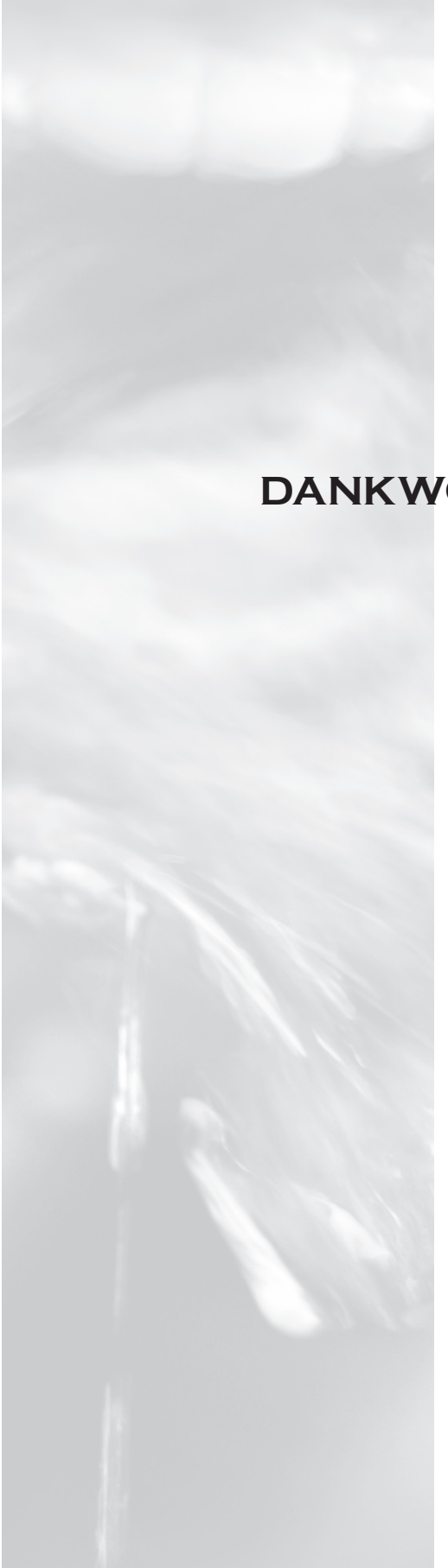

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LIST OF PUBLICATIONS

OVERVIEW SCIENTIFIC PUBLICATIONS

1. **Bots CP**, Brand HS, Veerman ECI, Valentijn-Benz M, Van Amerongen BM, Valentijn RM, Vos PF, Bijlsma JA, ter Wee PM, Nieuw Amerongen AV. The management of xerostomia in patients on hemodialysis: comparison of artificial saliva and chewing gum. *Oral Diseases (in press)*

2. **Bots CP**, Brand HS, Veerman ECI, Valentijn-Benz M, Van Amerongen BM, Valentijn RM, Bijlsma JA, ter Wee PM, Nieuw Amerongen AV. Reply from the authors. *Kidney Int* 2005; 67: 1192-1193

3. **Bots CP**, Poorterman JHG, Brand HS, Kalsbeek H, Van Amerongen BM, Veerman ECI, Nieuw Amerongen AV. The oral health status of dentate patients with chronic renal failure undergoing dialysis therapy. *Palliative Medicine* 2005; 19: 202-207

4. **Bots CP**, Brand HS, Veerman ECI, Valentijn-Benz M, Van Amerongen BM, Valentijn RM, Vos PF, Bijlsma JA, ter Wee PM, Nieuw Amerongen AV. Chewing gum and a saliva substitute alleviate thirst and xerostomia in patients on hemodialysis. *Nephrol Dial Transplant* 2005; 20: 578-584

5. **Bots CP**, Brand HS, Veerman ECI, Valentijn-Benz M, Van Amerongen BM, Valentijn RM, Vos PF, Bijlsma JA, ter Wee PM, Nieuw Amerongen AV. Interdialytic weight gain in patients on hemodialysis is associated with dry mouth and thirst. *Kidney Int* 2004; 66: 1662-1668

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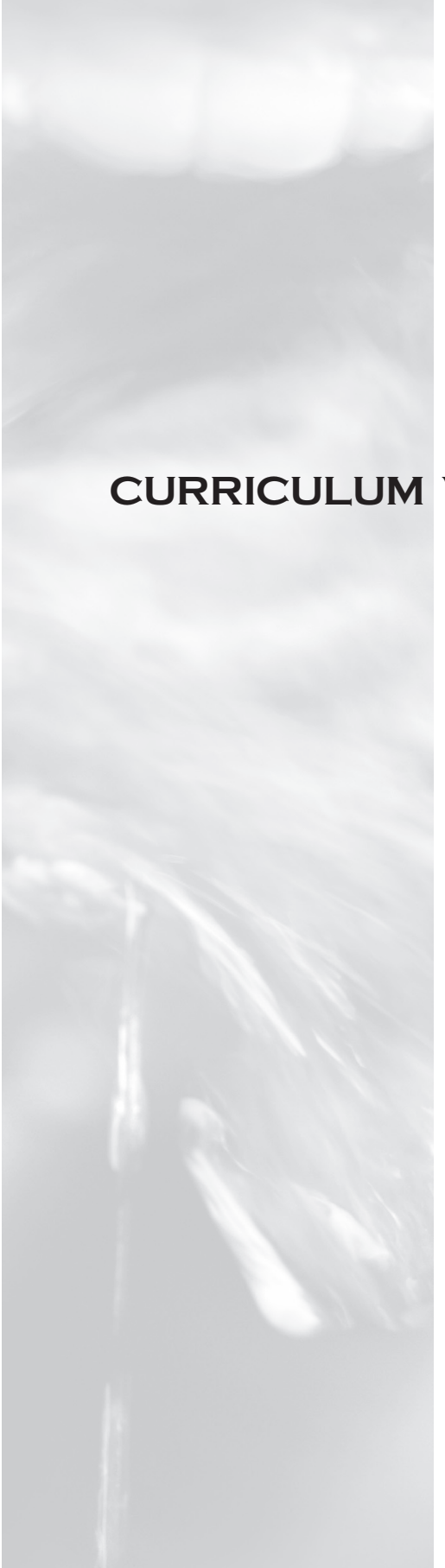

CURRICULUM VITAE

Casper P. Bots was born on June 5th 1974 in Wargea, Boarnsterhim, Friesland, the Netherlands and graduated from the secondary school at the Christelijk Lyceum in Gouda in 1993. In 1994, he started to study dentistry at the Academic Center for Dentistry Amsterdam (ACTA), the University of Amsterdam. He has been president of the studentscounsil and general secretary of the Educational Committee at ACTA (Opleidingscommissie). From 1996-1999, he was treasurer of the newly instituted Dutch Dental Students Association (SISO tandheelkunde) and actively involved in the European Dental Students Association (EDSA). Moreover, he was editor of the EDSA Magazine, general secretary and president of the EDSA. As a peer reviewer he participated in the 'DentEd international program' of the Association for Dental Education in Europe (ADEE) and reviewed curricula in several European dental Schools.

In 1998, he was involved in a research project at the department of cariology, Karolinska Institute, Stockholm, Sweden under supervision of prof. dr. Folke Lagerlöf. Aim of the study was to quantify the effects of fluoride on the erosive effects of malic acid. In March 1999, he started working as student-assistant at the department of Oral Biochemistry of ACTA. During several years, he has been working as free-lance journalist for the daily newspaper 'Algemeen Dagblad', 'Tandartspraktijk' and the 'Nederlands Tandartsenblad (NT)'. Since 2002, he is member of the NT advisory board of the Dutch Dental Association (NMT). From 1999-2000, he participated as a student – on behalf of the Chamber of Dentistry (Kamer Tandheelkunde) of the Association of Universities in the Netherlands (VSNU) – in the advisory board regarding the 'Capacity in Oral Care' for the Ministery of Health, Welfare and Sport.

Casper Bots received his dental degree in March 2000 and started his PhD program at the department of Dental Basic Sciences, section Oral Biochemistry at ACTA under supervision of prof. dr. Arie van Nieuw Amerongen. In April 2000 he received the Pierre Fauchard Academy Annual Scholarship Award for the academic achievements and board activities in dentistry. He has been staff member at the Saliva Clinic at ACTA, and member of the promovendi counsil from 2001-2003. During the PhD program, he finished his Msc in Epidemiology at the EMGO institute under supervision of prof. dr. Maarten Boers from the department of Clinical Epidemiology and Biostatistics at the Free University Medical Center, Amsterdam. In Oktober 2004, he received the 'VMTI award' from the Association of Medical Dental Interaction for his publication in Kidney International.

Besides his academic career, he has been working as dentist at the medical department of a penitentiary in Haarlem, and as general practitioner in Amersfoort and Bunschoten-Spakenburg.

Casper Bots is married to Nelleke van 't Spijker and has two children, Henrieke and Freerk.

ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ACTA	Academic Center for Dentistry Amsterdam
AQP	Aquaporines
CAPD	Continuous Ambulantory Periotoneal Dialysis
CCPD	Continuous Cycler-Assisted Periotoneal Dialysis
CH-SWS	Chewing stimulated whole saliva
CRF	Chronic Renal Failure
DBP	Diastolic Blood Pressure
DIAL	Dialysis
DMFS	Decayed Missing Filled Surfaces
DMFT	Decayed Missing Filled Teeth
DS	Decayed Surfaces
DT	Decayed Teeth
DTI	Dialysis Thirst Inventory
EDTA-ERA	European Dialysis and Transplantation Association-European Renal Association
ELISA	Enzyme-Linked Immunosorbent Assay
ESRD	End Stage Renal Disease
FS	Filled Surfaces
FT	Filled Teeth
HD	Hemodialysis
IgA	Immunoglobulin A
IOT	The Netherlands Institute for Dental Sciences
IWG	Interdialytic Weight Gain
KDQOL	Kidney Disease Quality of Life
KDQOL-SF	Kidney Disease Quality of Life- Short Version
Kt/V	Removal of urea by dialysis a week
LO-P	Liquorice Original
LPA	Level of Periodontal Attachment
MS	Missing Surfaces
MT	Missing Teeth
NECOSAD	Netherlands Cooperative Study on Adequacy of Dialysis
NTx	Renal transplantation
PD	Peritoneal dialysis
PM-P	Freedent Peppermint
PM-S	Orbit Peppermint
PM-T	Extra Peppermint
QoL	Quality of Life
RKZ	Rode Kruis Ziekenhuis

SBP	Systolic Blood Pressure
SD	Standard Deviation
S-IgA	Secretory Immunoglobulin A
SM-P	Freedent Sweetmint
SOHI	Simplified Oral Hygiene Index
SWS	Chewing Stimulated Whole Saliva
TDS	Thirst Distress Scale
UWS	Unstimulated Whole Saliva
VAS	Visual Analogue Scale
VUMC	Vrije Universiteit Medical Center
WF-P	Freedent Winterfresh
WF-S	Orbit Winterfresh
WF-T	Extra Winterfresh
XI	Xerostomia Inventory